ANNUAL REVIEW OF PHYSIOLOGY

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ANNUAL REVIEW OF PHYSIOLOGY

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PREFACE

That the *Annual Review of Physiology* is keenly aware of its responsibility for achieving a truly international scope in authorship and coverage is a recurrent theme in these prefaces. We make no apology this year in reasserting this aim. We hold with Julian Huxley[1] that the major ethical problem of our time, on which we will be judged by history, is to achieve global unity for man. As the world threatens to fall irrevocably into two armed camps, the need to assert, and where possible to implement by example, the basic unity of mankind becomes ever more pressing. Science is among the few fields of human activity where this remains possible. The meeting of the International Physiological Congress of Physiology at Oxford last summer, participated in by men and women of many nations, including those with the most divergent political and economic philosophies, demonstrated that such differences are no obstacles in the co-operative activity of science.

In this volume the *Annual Review* has achieved international authorship only in small degree. The four reviews from overseas are all from the British Commonwealth: two from England, and one each from Australia and New Zealand. The reviews which two of our Russian colleagues were to have contributed failed to reach us; that of Assistant Commissar N. Propper-Graschenkov on Cutaneous Sensation has been, at his request, deferred to the next volume. The Board of Editors will in the future continue its efforts to secure contributions from physiologists of highest rank throughout the world. The degree to which we can achieve this goal will reflect the growth or decay of sanity in international affairs.

It is regrettable that, even in our science which is overwhelmingly devoted to the mitigation of the results of human brutality rather than to their promotion, the free international flow of the results of fundamental scientific investigation continues to be impeded by governments at home and abroad which, to gain a problematical mite of "security" sacrifice a treasured ideal of science. Whatever may be the merits of suppression of technical military application of physiological knowledge, acquiescence by scientists in this tendency as it applies to advances in our basic understanding of nature is a betrayal of their responsibilities to mankind.

[1] Julian Huxley, *Touchstone for Ethics* (Harper & Bros., New York, N. Y., 1947).

Several of the chapters listed in the preliminary announcement of this volume have not become available: Professor L. H. Newburgh was prevented by illness from completing his review of Water Metabolism; Professor A. J. Carlson's many duties did not permit him to survey the wartime studies on Nutrition; while Dr. R. A. Phillips' task of organizing the work of the U. S. Naval Medical Research Unit in Cairo forced him to defer his review of Kidney Function to the next volume, in which the advances made in the two-year period will be considered.

The Board has adopted a new procedure in the selection of prospective authors. Contributors to each volume are now invited to submit the names of several persons they deem most competent to write on the same topic for the subsequent volume. To these names are added those suggested by the Board members, the Editorial Staff, and others. Selections are commonly but not invariably made from the resulting list. The Board invites any interested biological scientists to submit suggestions for authors (or concerning other aspects of the *Review*) at any time to the Editor. Such suggestions will be included in the panel from which selection of authors will be made.

In order to encourage the dispatch of reprints to contributors we present on the next three pages the names and addresses of those who are expected to participate in authorship of forthcoming volumes of the three *Reviews*.

The retirement of Professor Carlson from the Editorial Committee is a source of deep regret to us who have, as his colleagues, profited by his wide knowledge of the capacities of active workers in our science and who have enjoyed his salty wisdom and humor. We welcome as his successor Professor Robert Pitts of Syracuse University.

It is a pleasure to acknowledge the loyal services of our efficient editorial and secretarial assistants, Barbara Davey, Ruth Swan, Doreen Booth, Jane Gerhart, Dorothy Bauck, Virginia Lee, and Cornelius Cotter, and once again to express our appreciation of the work of the George Banta Publishing Company in the preparation of this volume.

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TOPICS AND AUTHORS

ANNUAL REVIEW OF MICROBIOLOGY
VOLUME II, 1948

Genetics of the Fungi—Lindegren, C. C., Department of Botany, Washington University, St. Louis 5, Missouri

Metabolism of Microorganisms—Gunsalus, I. C., New York State College of Agriculture, Cornell University, Ithaca, New York

Metabolism of Protozoa (Malarial Parasites)—Moulder, J. W., Department of Bacteriology, The University of Chicago, Chicago 37, Illinois

Growth Factors for Microorganisms—Koser, S. A., Department of Bacteriology, The University of Chicago, Chicago 37, Illinois

Nitrogen Fixation—Virtanen, A. I., Biochemical Institute, Helsinki, Finland

Antibiotics—Bailey, J. H., and Cavallito, C. J., Sterling-Winthrop Research Institute, Rensselaer, New York

Mode of Action of Chemotherapeutic Agents—Hotchkiss, R. D., The Rockefeller Institute for Medical Research, 66th Street and York Avenue, New York, New York

Complement—Ecker, E. E., Institute of Pathology, Western Reserve University, 2085 Adelbert Road, Cleveland, Ohio

Nature of Antibodies—Pauling, L., and Campbell, D. H., Department of Chemistry, California Institute of Technology, Pasadena, California

Inheritance of Immunity in Animals—Gowen, J. W., Department of Zoology, Iowa State College, Ames, Iowa

Yeasts—Mrak, E. M., Division of Food Technology, University of California, Berkeley 4, California

Microbiology of Soil—Smith, N. R., Bureau of Plant Industry, U. S. Department of Agriculture, Beltsville, Maryland

Pathogenic Streptococci—Dingle, J. R., and Rammelkamp, C. H., Jr., Department of Preventive Medicine, Western Reserve University School of Medicine, Cleveland, Ohio

The Neurotropic Viruses—Schultz, E. W., Department of Bacteriology, Stanford University, California

Spirochaetes—Davis, G. E., Rocky Mountain Lab., U. S. Public Health Service, Hamilton, Montana

The Microbiology of Water and Sewage—Smit, J., Landbouw Hoogeschool, Wageningen, Holland

Chemical Disinfectants—Wyss, O., Department of Bacteriology, University of Texas, Austin 12, Texas

Bacteria as Plant Pathogens—Burkholder, W. H., Department of Plant Pathology, Cornell University, Ithaca, New York

TOPICS AND AUTHORS

ANNUAL REVIEW OF PHYSIOLOGY
VOLUME XI, 1949

Permeability—Teorell, T., Department of Physiology, University, Upsala, Sweden

Bioelectric Potentials in the Nervous System and in Muscle—Lloyd, D. P. C., Rockefeller Institute for Medical Research, 66th Street and York Avenue, New York 21, New York

Radiation—Nims, L. F., Yale University School of Medicine, Aero Medical Research Unit, 333 Cedar Street, New Haven, Connecticut

Developmental Physiology—Schechtman, M., Department of Zoology, University of California at Los Angeles, Los Angeles 24, California

Physiological Effects of Heat and Cold—Haterius, H. O., Department of Physiology, Boston University School of Medicine, Boston, Massachusetts

Respiration—Wyss, O., Department of Physiology, University of Geneva, Geneva, Switzerland

Muscle—Sandow, A., Department of Biology, Washington Square College, New York University, New York 3, New York

Digestive System—Thomas, J. E., and Friedman, M. H. F., Jefferson Medical College, 1019 Walnut Street, Philadelphia, Pennsylvania

Liver—Hoffbauer, F. W., Department of Medicine, Univ. of Minnesota, Minneapolis 14, Minnesota

Hematopoiesis—Wintrobe, M., and Cartwright, G. E., Department of Medicine, University of Utah, Salt Lake City, Utah

Lymphatic System—White, A., Yale University Medical School, 333 Cedar Street, New Haven, Connecticut

Peripheral Circulation—Ogden, E., University of Texas Medical School, Galveston, Texas

Heart—Robb, J. S., Department of Pharmacology, College of Medicine, Syracuse University, 761 Irving Ave., Syracuse, New York

Kidney—Phillips, R. A., NAMRU #3, Cairo Egypt, c/o Chief of Naval Operations (Op-32), Mail and Dispatch Section, Navy Department, Washington 25, D.C.

Somatic Functions of the Nervous System—Magoun, H. W., Department of Anatomy, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, Illinois

Visceral Functions of the Nervous System—Youmans, W. B., Department of Physiology, University of Oregon Medical School, Portland, Oregon

Electrical Activity of the Brain—Walter, W. G., Burden Neurological Institute, Stoke Lane, Stapleton, Bristol, England

Special Senses–Vision—Talbot, S. A., Johns Hopkins Hospital, Baltimore, Maryland

Special Senses–Hearing—Walzl, E. M., Johns Hopkins School of Medicine, Baltimore, Maryland

Physiological Psychology—Harlow, H., Department of Psychology, University of Wisconsin, Madison, Wisconsin

Metabolic Functions of the Endocrine System—Barker, S. B., Department of Physiology, State University of Iowa, Iowa City, Iowa

Reproduction—Catchpole, H., Department of Pathology, University of Illinois, Chicago, Illinois

Pharmacology—Moe, G. K., Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan

TOPICS AND AUTHORS

ANNUAL REVIEW OF BIOCHEMISTRY
VOLUME XVIII, 1949

Biological Oxidations and Reductions—Preisler, P. W., Department of Biochemistry, Washington University Medical School, St. Louis, Missouri

Proteolytic Enzymes—Smith, E. L., Department of Biochemistry, School of Medicine, University of Utah, Salt Lake City 1, Utah

Nonoxidative, Nonproteolytic Enzymes—Myrbäck, K., Biokemiska Institutet, Stockholm 6, Sweden

The Chemistry of the Carbohydrates—Bell, D. J., School of Biochemistry, Tennis Court Road, Cambridge, England

The Chemistry of the Lipids—Lovern, J. A., Torry Research Station, Aberdeen, Scotland

The Chemistry of Amino Acids and Proteins—Lundgren, H. P., and Ward, W. H., U. S. Department of Agriculture, Western Regional Research Laboratory, Albany 6, California

Nucleoproteins, Nucleic Acids, and Derived Substances—Davidson, J. N., Department of Biochemistry, The University, Glasgow W. 2, Scotland

Phosphorus Compounds—Lipmann, F., and Kaplan, N. O., Biochemical Research Laboratory, Massachusetts General Hospital, Boston, Massachusetts

Carbohydrate Metabolism—Wood, H. G., Department of Biochemistry, Western Reserve University, Cleveland, Ohio

The Metabolism of the Lipids—Lehninger, A. L., Department of Biochemistry, University of Chicago Medical School, Chicago, Illinois

Chemistry of Neoplastic Tissue—Boyland, E., The Chester Beatty Research Institute, The Royal Cancer Hospital, Fulham Road, London, S. W. 3, England

Metabolism of Proteins and Amino Acids—Neuberger, A., The National Institute for Medical Research, Hampstead, London, N. W. 3, England

Mineral Metabolism—McClure, F. J., U. S. Public Health Service, Washington, D.C.

The Chemistry of the Hormones—Meischer, K., and Wettstein, A., Ciba Limited, Basle, Switzerland

Fat-Soluble Vitamins—Harris, P. L., Distillation Products, Inc., 755 Ridge Road West, Rochester, New York

Water-Soluble Vitamins—Stokstad, E. L. R., Lederle Laboratories, Pearl River, New York

Nutrition—Keys, A., Laboratory of Physiological Hygiene, University of Minnesota, Stadium South Tower, Minneapolis, Minnesota

Metabolic Inhibitors—Winzler, R. J., Department of Biochemistry, University of Southern California Medical School, Los Angeles 7, California

Chemistry of Antibiotics—Wintersteiner, O., and Dutcher, J. D., The Squibb Institute for Medical Research, New Brunswick, New Jersey

Biochemistry of Insects—Wigglesworth, J. B., Department of Zoology, University of Cambridge, Downing Street, Cambridge, England

Nitrogenous Constituents of Plants—McCalla, A. G., Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada

Organic Acids in Plants—Bennett-Clark, T. A., King's College, Strand, W.C. 2, London, England

Mineral Nutrition of Plants—Wadleigh, C. H., U. S. Department of Agriculture, Riverside, California

Dormancy in Plants—Bennett, J. P., Department of Botany, Univ. of California, Berkeley, California

Genetics—Beadle, G. W., Department of Biology, California Institute of Technology, Pasadena, California

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PHYSICAL PROPERTIES OF PROTOPLASM

By F. O. Schmitt and A. R. T. Denues*
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This necessarily brief review deals with the literature in the period from August, 1944 to August, 1947 on subjects traditionally included in the field of the assigned topic. However, emphasis is placed on several promising trends, particularly the application of information from precise physical investigations of model systems (interfacial films, coacervates, tactoids and protein-enzyme systems), and the interpretation of observable physical properties of protoplasmic systems in terms of their molecular structure.

Nucleus and Chromosomes

Micrurgical studies of the chromosomes of *Chironomus* salivary gland cells [D'Angelo ('46)] indicate that normal chromosomes *in situ* are not "sticky," being separated by a jellied nuclear matrix. They are easily deformable and reversibly extensible, to five times original length in the nucleus and to as much as twenty-five times when isolated in a favorable medium. Longitudinal fibrils showing nodules corresponding to the bands were dissected from the chromosomes and were also demonstrated by expelling chromosomes from close-fitting pipettes, resulting in fraying into longitudinal fibrils. A delicate elastic membrane around the chromosomes was demonstrated. The chromosomes retained their form even in chemically hyalinized nuclei. Monné ('45) believes that lipids, chiefly cholesterol, synthesized by euchromatin endow chromosomes with the ability to swell extensively without dissolving. In frog and salamander germinal vesicles, Duryee ('47) observed a highly elastic, gelatinous "chromosome frame" that separates the chromosomes; this gel forms the first maturation spindle on breakdown of the germinal vesicle. The polyphasic nucleoli were shown to behave as coacervates.

Cytological studies of fixed material have not yet led to complete agreement on such fundamental matters as the nature of

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the chromonema and chromomeres [Ris ('45); Hinton ('46 a); Manton ('45); Ruch ('45); Slizynski ('46, '47)], to say nothing of the gene [Frey-Wyssling ('44); Muller ('47)]. Some advance has been made with polarized light methods. Pfeiffer ('44) measured the birefringence of chromatin threads in *Paludina* spermatids and of α-thymonucleic acid and noted a partially reversible elasto-optical effect superimposed on the intrinsic birefringence of the chromatin. Caspersson's ('40) statement that measurement of ultraviolet dichroism is more sensitive than birefringence methods for determination of nucleic acid orientation in chromosomes was disputed by Schmidt ('41) and by Pfeiffer ('41). The latter determined refractive indices of *Chironomus* chromosomes by the Becke line imbibition method and the scattering angle [after Frey-Wyssling ('43)]; values for nucleic acid orientation so obtained agreed well with those deduced from birefringence, substantiating the high sensitivity of the birefringence method [Pfeiffer ('46)]. Mazia ('47) studied nucleoprotein fibers, produced by compression of monolayers, as a model of chromosome structure. Similarities of response to enzymes and x-rays led him to speculate on similarities of ultrastructure. Electron microscope studies of chromosome structure [Clark, Barnes & Baylor ('42); Clark, Quaife & Baylor ('43); Elvers ('43); Buchholz ('47)] have so far added little to our knowledge.

Cytoplasm and Its Constituents

Reversible gelation.—The value of hydrostatic pressure as a tool for the study of sol-gel transformations and other colloidal properties of protoplasm has been demonstrated. Pease ('46) made effective use of quantitative methods [Marsland ('39); Marsland & Brown ('42)] in relating changes in viscosity to applied pressure in meiotic divisions of *Tradescantia* pollen mother cells. He found that pressures of 5000 to 7000 lbs./in.^{2} liquefy the spindle reversibly. Condensed chromosomes are softened by such pressures but are liquefied by 15,000 lbs./in.^{2}. Because high pressures affected only prophase chromosomes, the liquefaction was attributed to the matrix material. Pease concluded that a gel structure in the spindle is essential for anaphase movement; that traction fibers merely provide semielastic connections[1] between chromosomes and the

[1] This is not necessarily in disagreement with Schmidt's ('39) polarized light observations on spindle fibers.

moving spindle mass; and that sol-gel-sol transformations provide the force for spindle retraction of chromosomes. The protein denaturing action of pressure may be important in the interpretation of such biological effects [Johnson & Campbell ('45,'46); Campbell & Johnson ('46)].

Valuable clues about the status of cytoplasmic proteins were obtained by application of the microtensiometer technique of Kopac ('44, '47). The spontaneous Devaux effect at the interface between injected oil and aqueous phases of cytoplasm is not observed if the cytoplasm is intact but is evident very soon after cytolysis, indicating surface denaturation of the released proteins. Kopac suggests that resistance of cytoplasmic proteins to interfacial denaturation may be correlated either with their resistance to proteolysis or with the presence of molecules stabilizing the protein structure.

In an excellent review of theories of amoeboid movement, De Bruyn ('47) concludes that contractility of the plasma gel plays a dominant role. In a modern version of the earliest theories of contractile reticula, contraction is ascribed to a rearrangement (folding) of a three-dimensional network of interlinked protein chains. Unfortunately little is known about the chemical properties of these proteins or of the mechanism of energy coupling. In metabolic studies, using the colorimetric method of Holter ('45), Andresen & Holter ('45) found that starvation of *Chaos chaos* markedly reduces cytoplasmic viscosity and cell volume. Development of the "Diver Balance," capable of weighing single living cells without damage [Zeuthen ('47)], promises further technical advances in this field.

Rhythmic flow and torsion of myxomycete cytoplasm, measured by observing a needle adhering to a free-hanging strand, have been further reported by Seifriz ('46). He attributes the torsional effects to molecular asymmetries or to spiral molecular orientations.

Continuing his centrifugation studies of *Elodea*, Northen ('46) found that treatment with sucrose, potassium chloride and other substances decreases cytoplasmic viscosity; the effect was attributed to "dissociations of protoplasmic proteins."

Structural properties.—Advances in the investigation of the ultrastructure of protoplasm have been reviewed by Schmidt ('42, '43), and Schmitt ('44, '45). An analysis of cytoplasmic birefrin-

gence in a variety of secreting and absorbing epithelial cells was made by Hillarp & Olivecrona ('46). They deduce the existence of filaments, oriented in the secreting axis of the cell, composed of fibrous proteins parallel to and of lipids normal to the filament axis. This deduction is strengthened by the directional shrinkage observed when the tissues were heated. The filaments are considered an expression of the molecular structure of the ground cytoplasm. Phase contrast microscopy [Bennett *et al.* ('46); Richards ('46); Martin ('47)] has been useful in visualizing protoplasmic structure in the living state. For example, Brice, Jones & Smyth ('46) were able clearly to observe structure in the Golgi apparatus of fresh unstained cells which agrees well with that observed after fixation and staining [Hibbard ('45)]. While electron microscopy has revealed important information on cell parts and isolated components, its application to whole cells[2] or tissues requires the development of accessory techniques, particularly that of very thin sectioning [Sjöstrand ('43); Krause ('44); Claude & Fullam ('46); Fullam & Gessler ('46); Gessler & Fullam ('46)].

The submicroscopic structure of chloroplasts has been studied in polarized light [Pfeiffer ('43); Frey-Wyssling & Wuhrmann ('47)]. If the alleged lamellar structure is verified it may be significant that this type of structure is present also in the light receptors (retinal rods) of animals [Schmidt ('37)]. Volume contractions in chloroplasts in response to water flow through the cell are ascribed to a water-extractable material in the chloroplast by Osterhout ('46 a, b; '47).

Cortical layers and surface structures of marine eggs have been extensively studied in the laboratories of Runnström in Stockholm and of Monroy in Naples. Runnström, Monné & Broman ('44), and Runnström & Monné ('45 a, b) studied the surface layers and the formation of the fertilization membrane in sea urchin eggs with the aid of polarizing and dark field microscopy and the "hypertonicity test." General discussions of this work are given by Runnström, Monné & Wicklund ('46) and by Monné ('46). Previous observations that the cortical layer contains lipid molecules radially oriented and proteins tangentially oriented are extended to cells subjected to a variety of conditions. Hypertonic solutions cause

[2] Excellent electron micrographs of cells grown in tissue culture have been obtained by Porter, Claude & Fullam ('45).

wrinkling of the cell surface which may become smooth in the presence of calcium and of a substance extractable from the egg. Liquefaction of the surface is regarded as a step in the activation process. The action of detergents and other agents is considered by Monné ('47 b) and Monné & Wicklund ('47). Monroy ('45), Monroy & Monroy Oddo ('45, '46) and Monroy & Montalenti ('46, '47) had attributed the positive birefringence (with respect to the radius) of the cortical layer of sea urchin eggs to smectic layers of lipids; the values of 0.012 to 0.015 obtained for this birefringence, due presumably to phospholipids and cholesterol, would indicate both a high degree of orientation and a high concentration of lipids. Subsequently [Monroy ('47)], evidence was given for the presence of submicroscopic protein particles tangentially oriented in the cortex, in agreement with Monné and Runnström. Fertilization altered the lipid-protein association. A cyclic variation of cortical birefringence was seen with mitotic division, maximum orientation occurring between metaphase and telophase. These data are to be correlated with sol-gel transformations previously noted and with the recent work of Carlson ('46) on cytoplasmic viscosity. Using Brownian movement of mitochondria as a criterion, he found that the viscosity of grasshopper neuroblasts decreases from late prophase until early anaphase; he regards this as typical of many cells and attributes it to the decrease of cytoplasmic pentose nucleic acid (of relatively high viscosity), presumably attending its conversion to desoxyribose nucleic acid in the chromosomes.

Cell membranes and permeability.—Little progress, exclusive of isotope and electrical studies, can be reported on the investigation of the physical properties of cellular membranes and their relation to permeability.

Collander ('47) considered the solvent power of various organic liquids and discussed its bearing on the structure and composition of the plasma membrane.

The physical properties of the nonaqueous films covering the vacuoles of several algae were studied by Osterhout ('44, '45). Wilber ('46) found the membranes surrounding the food and contractile vacuoles in *Pelomyxa* to be discrete, elastic and semipermeable.

As the plasma membrane, and probably other protoplasmic membranes, are very thin (*ca.* 100 Å) films, studies of the proper-

ties of such films are of considerable interest [Rideal ('45); Danielli ('45 b); Bull ('47)]. Particularly desirable are investigations of films at liquid-liquid interfaces.

Langmuir & Schaefer's ('43) experiments on the ability of a compressed monolayer to reduce the rate of penetration of water may be cited as illustrative of the importance of film studies in problems of permeability. In explaining the rather striking effects, the authors considered the nature of the stresses within the monolayer which constitute an energy barrier to water penetration (angle of tilt, polar-polar and nonpolar interaction between adjacent molecules, crystal-like properties of the film, effect of water molecules on polar interactions and so on).

Extraneous Coats and Intercellular Matrix

Extraneous coats and intercellular matrices contribute importantly to the physical properties and permeability of free cells and tissues. Extraneous coats have been discussed in some detail by Chambers ('40) and Kopac ('40); Runnström *et al.* were concerned with optical studies of the external membranes of marine eggs before and after fertilization.

Connective tissue is the most widely distributed intercellular material, yet its role in physiological and pathological processes is very poorly understood. The collagenous component has been the object of considerable chemical and structural investigation but the "ground substance" was, until recently, but a poorly defined morphological entity. The matrix properties of ground substance are determined by the state of polymerization of its mucopolysaccharides, chiefly hyaluronic acid and chondroitin sulfuric acid. The native polysaccharides have particle weights as high as 500,000 [see Meyer ('45) and Morgan ('46)] but may be depolymerized and hydrolyzed by enzymes (hyaluronidase, lysozyme). The depolymerization is accompanied by a marked drop in viscosity and streaming birefringence *in vitro* and a dramatic increase in permeability of connective tissue *in vivo*. This enzyme-conditioned change of structural polysaccharides has been linked with bacterial invasiveness [Duran-Reynals ('42); Fleming ('46); Haas ('46)], with penetration of egg membranes by the sperm, with capillary permeability, sedimentation rate and a variety of pathological conditions. An excellent summary of this literature has been prepared by the Schering Corporation ('47).

MORPHODYNAMICS

Growth and differentiation.—In a provocative theoretical discussion of selective cell and tissue affinities as they relate to the problem of specificity in growth and differentiation, Weiss ('47a) emphasizes the significance of ultrastructure and "molecular ecology" in the modern approach to such complex biological problems. His previous demonstration of the role of fibrous materials, given off by tissue fragments, in determining the growth of nerve fibers in tissue culture [Weiss ('45)] illustrates how this approach may be fruitfully applied experimentally.

The physical and chemical properties of the surface layer and of the cellular inclusions of amphibian eggs were extensively investigated by Holtfreter ('43, a, b; '44; '46 a, b, c) with reference to morphogenesis in general and to the mechanics of gastrulation in particular. W. H. Lewis ('47), who has long stressed the importance of the plasmagel in embryogenesis, suggests that invagination (or evagination) is due to tension changes in the contractile superficial gel layers of adherent epithelial cells; invagination occurs on the side of greater tension. A dorsoventral gradient of water content and the resultant condensation of the texture of cytoplasmic fibrils are held responsible for the initiation of invagination in the vegetal region of the eggs of *Echinocardium* and *Brissopsis* by Monné ('47 a).

The role of mechanical stresses in determining orientation of tonofibrils of vertebrate epidermal cells is discussed by Schmidt ('46), who speculates on the polymerization-like process by which such fibrils are formed. Similarly, Picken, Pryor & Swann ('47) suggest that mechanical forces during deposition determine preferred orientations of fibrils in cuticular membranes.

The extensive literature on the role of electric fields in growth processes, particularly in plants, has been reviewed in a recent book by Lund and collaborators ('47).

The form of the simpler cells has been discussed by Danielli ('45 a) with respect to physical, particularly surface, forces. The geometry of cell shape has been considered by Glaser ('45), F. T. Lewis ('46), Matzke ('46, '47) and Matzke & Nestler ('46).

Form of nerve.—Recent observations have brought to light certain unsuspected physical properties of nerve fibers. Weiss ('43, '44) and Weiss & Taylor ('44) observed that proximal to an applied constriction the axons greatly distend while distal to the constric-

tion the fiber diameter decreases; on release of the constriction the swellings spread distally. Weiss concludes that there is a continuous flow of axoplasm peripherally from the cell body.[3] From studies of the properties of cut nerve fibers, Young ('42, '44a) likewise inferred a continuous pressure and flow from the cell body along the axon, with fluid loss through the surface. The pressure is presumably osmotic, resulting from ribonuclease breakdown of nucleotides (chromatolysis), as demonstrated by Gersh & Bodian ('43). This flow constitutes the "trophic" influence of the cell body, maintaining the fiber type. Weiss ('47 b) considers that the axoplasm moves distally more or less as a coherent mass and that the materials—chiefly proteins—are oxidatively removed; hence the need for constant replenishment from the synthetic center, the cell. The influences of interfacial tensions and other physical factors on the structure of myelinated nerve fibers are discussed by Young ('44b, '45 a) and summarized by him in a stimulating chapter of a book dedicated to D'Arcy Thompson [Young ('45 b)].

It is claimed by Flaig ('47) that electrical stimulation of the squid giant fiber prevents outflow of axoplasm when the fiber is cut. He believes that stimulation increases the viscosity of axoplasm by shifting the sol-gel equilibrium.

Fibrous protein systems.—The structure of the fibrous proteins has been further studied with polarization optics, x-ray diffraction and electron microscopy [see Astbury ('45, '46); Rudall ('46); Bear ('44 a, b; '45); Schmitt ('44, '45); Nowacki ('44); Fankuchen & Mark ('46); Jakus & Hall ('47)]. These advances provide a basis for a better understanding of the physical properties not only of the more inert, supporting structures but also of the physiologically active fibers. Previous concepts emphasized changes of configuration of polypeptide chains to explain contractility and extensibility. However, it is now recognized that many reactive fibrous proteins consist of globular molecules in linear array and that their physical properties depend on a reversible globule-fiber transformation sensitive to pH, ionic environment and enzymes. The globule-fiber transformation[4] has been demonstrated with actin

[3] Fluid flow was also indicated in the endoneurial spaces of nerves [Weiss ('43); Weiss & Davis ('43); Weiss, Wang, Taylor & Edds ('45)].

[4] Denaturation of globular protein molecules involves unfolding into more linear fibrous forms. Eyring, Johnson & Gensler ('46) considered this process in the case of reversible inactivation of enzymes and generalized on its role in gene and virus action.

[Straub ('42); Jakus & Hall ('47)], insulin [Waugh ('44, '45, '46)], hemocyanin [Pickels & Anderson ('46); Brohult ('47)] and virus particles [Wyckoff ('46)]. Even more stable fibers, such as keratin, have been considered linear arrays of globular particles [Farrant, Rees & Mercer ('47)].[5]

Perhaps the most dramatic example of the response of fibrous proteins to changes in chemical environment is provided by recent investigations of muscle proteins [Szent-Györgyi ('45, '46, '47); Buchthal ('47)]. Study of physical changes in threads of isolated proteins has provided both crucial evidence on the mechanism of muscle contraction and a pattern for study of other fibrous protoplasmic systems.[6] The importance of energy-rich phosphate compounds, particularly adenosine triphosphate, in muscular contraction has long been recognized; it may be hoped that the details of the energy-work coupling process may soon become better understood. In a stimulating article on the relation of "macroenergic compounds" to cell function, Engelhardt ('45) visualizes the existence of "osmotic enzymes" of the kidney and "visual enzymes" of the retina! While such systems may exist, much basic biochemical and biophysical work is needed to clarify their properties.

Some Biophysical Problems

From work on the physical properties of protoplasm and related colloidal systems there have been posed a number of challenging physical problems dealing with various aspects of distance action.

The nature of forces responsible for large (order of hundreds of Angstrom units) but regular separation of particles in certain tactoids and coacervates[7] remains relatively obscure. Such systems, though dilute with respect to the dispersed particles, possess a high degree of structural regularity. Verwey & Overbeek ('46) and Verwey ('47) offered a revision of a previous theory (Verwey & Overbeek) involving long-range action of London-Van der Waal's

[5] The globular particles were observed in electron micrographs of gold shadowed specimens. Owing to the tendency of gold to migrate and to form aggregates, further evidence for the existence and size of the particles is desirable.

[6] Heilbrunn & Wiercinski ('47) emphasize the value of studying living muscles rather than partial systems and adduce further evidence for the calcium release theory of stimulation.

[7] Sols of iron oxide [Zocher ('25)] and bentonite [Hauser ('45); Langmuir ('38)], dispersions of soaps [Dervichian & Lachampt ('45); Harkins, Mattoon & Corrin ('46); Ross & McBain ('46); Harkins ('47)] and lipids [Palmer & Schmitt ('41)], and certain virus tactoids [Bernal & Fankuchen ('41)].

attractive forces. A preliminary account was given by Levine ('46) of an alternative theory which provides for a minimum in the mutual free energy of the colloidal layers without introducing Van der Waal's forces. Whatever the eventual solution of the problem, it is important that biologists recognize the fundamental bearing of such ordering forces on the structure and properties of protoplasm.

Another problem involving distance action arose from Rothen's experiments ('45, '46, '47 a, b, c) with immunological and enzymatic reactions in thin films. He showed that a film of antigen is capable of specifically adsorbing homologous antibody molecules even when antigen and antibody are separated by an inert screening layer of stearate or Formvar. Similarly, albumin films are hydrolyzed by crystalline trypsin or pepsin, and the polysaccharide of pneumococcus III is hydrolyzed by a specific enzyme despite separation of enzyme and substrate by the inert film. Rothen concluded that the effective range of action in such systems is of the order of hundreds of Angstrom units rather than the short distance characteristic of ordinary chemical reactions. In explanation, he refers to the work of London ('37, '42, '43), who showed the relation between anisotropic bond polarizabilities and Van der Waal's forces and considered the forces between large molecules containing "electronic oscillators." These monopole forces are not additive but are highly specific and are particularly strong in conjugated systems when the oscillators are long and of relatively low frequency. Increasing the number of oscillating components should increase the distance through which they act.

Unless an alternative explanation of Rothen's experiments is found, the startling possibility that enzymes and other biologically active molecules may effect chemical action at distances comparable to the dimensions of many cellular structures must be reckoned with.[8]

Based on less specific evidence and patterned after the modern quantum theory of metals, are recent speculations concerning the possible transfer of energy by "electron continua" within or between large molecules. Denbigh ('44) pointed out that the polypeptide grid "would be expected to have an appreciable electron mobility over the full length of the molecules and along the

[8] Long-range forces are also invoked by Hinton ('46 b) to account for chromosome pairing; the distance involved in this case is of the order of micra!

axis of the protein fibre." He suggested that this may be of importance in nerve and muscle action [see also O. Schmidt ('43)]. Szent-Györgyi ('41, '47) considers that nonlocalized electrons associated with common energy levels in proteins and other biological components may account for transmission of chemical effects in genes, muscle fibers, indeed over large distances in whole cells and tissues and even through entire organisms, in health and disease! Evidence cited for common energy bands deals chiefly with phosphorescence and photoconductivity effects observed with proteins treated with certain dyes; phosphorescence with increased conductivity on illumination is taken as indicative of band structure [however, see Lewis & Kasha ('44, '45)]. While the biological application of this aspect of quantum theory may be premature, a beginning may be made by considering certain structurally favorable, biochemically definable entities.

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PHYSIOLOGICAL ASPECTS OF GENETICS[1]

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The biological sciences appear to be in the midst of a period of unprecedented progress. An important salient in the advance is the general recognition of the significance of genes in the economy of the organism. The change is largely one in point of view. Many biologists have for a long time appreciated the basic nature of the gene and its role in development and function, but these relatively enlightened individuals have for the most part belonged to a small group of specialists that has tended to remain in isolation. The restraining fences are now being broken down with gratifying rapidity. Biochemists have begun to think in terms of genes because it has been demonstrated to them not only that the chemical reactions which make up living systems are under the fairly immediate supervision of these units of inheritance, but also that genetics provides a powerful tool with which a great deal can be learned about metabolic systems. In bacteriology, too, one sees the effects of an altered point of view toward genetics. Only a few years ago a bacteriologist who so much as raised the question of the existence of genes in bacteria was regarded as a renegade and heretic by his more orthodox fellowmen. It has now become acceptable to speak of bacterial genes; in fact, a recognized field of bacterial genetics has grown up almost over night (1).

Several general reviews of the field of genetics have appeared since Danforth's (2) contribution to this series (3 to 8). British wartime achievements in genetics have been summarized in the first number of the new Journal *Heredity* (9). In the same issue is found a most valuable bibliography of genetic papers published in Italy and Germany during the war years, 1939 to 1945 (10). The eleventh volume of the Cold Spring Harbor Symposia on Quantitative Biology entitled *Heredity and Variation in Microorganisms* (11) constitutes a series of vivid expressions of the new viewpoints in genetics applied to bacteria, viruses and other microorganisms. The first volume of a series of annual reports on Symposia of the

[1] This review covers the period from January 1, 1946 to July 15, 1947.

Society of Experimental Biology (British) has just appeared (11a) It contains nineteen significant and timely papers on nucleic acids.

The present reviewer has chosen for special consideration several topics in physiological or chemical genetics in which it appears that particularly significant developments are taking place. Limitations in space as well as in time, industry and insight of the author have precluded adequate consideration of other lines of work that may in the long run prove to be of even greater significance. In this latter category are recent additions to our knowledge of chromosome chemistry. It is not now clear to the reviewer just what are the interrelations of the genoprotein-T of Stern *et al.* (12), the chromosin of Mirsky & Pollister (13, 14) and the chromosomin of the Stedmans (15). Progress continues to be made in immunogenetics as evidenced by the reviews of Irwin (16, 17), additional work on inherited cellular antigenes in pigeons and doves (18), and further interpretations of the data on *Rh* blood types in man (19, 20, 21). Additional experimental and theoretical consideration has been given to the phenomenon of position effect by Stern and his co-workers (22, 23), Gersh & Ephrussi (24), and by Goldschmidt (25). Among other advances in physiological genetics that cannot be adequately treated here are the determination of pigment-granule characteristics in a number of mouse coat-color types (26), the chromatographic fractionation of the red pigments of the *Drosophilia* eye (27), the relation of the eye pigmentation to protein composition in *Ephestia* (28), studies on multiple alleles and modifier genes (29, 30, 31), and the effect of infrared radiation on the effectiveness of x-rays in producing mutations (32).

Genes and Biosynthesis

Production and detection of biochemical mutations—During the past half dozen years many mutant strains of microorganisms with altered growth-factor requirements have been studied. The frequency with which these arise may be greatly increased by treatment with ionizing radiation, ultraviolet radiation, and certain chemicals. The method of producing and detecting growth-factor mutants in *Neurospora* has been described in detail by Beadle & Tatum (33). It consists in testing individually numerous strains for ability to grow on a minimal medium. Essentially the same method has been used extensively by Fries (34) for detecting mu-

tant strains in the Ascomycete *Ophiostoma*. Recently Fries (35) has developed a technique of filtering out and discarding the descendant mycelia of spores that germinate and grow on basal medium. In this way he has increased the frequency of the mutant strains among tested individuals by a factor of approximately eight. Because of the strong tendency to heterocaryon formation in *Neurospora* it seems unlikely that the Fries technique can be applied without modification in this organism. Lederberg & Tatum (36) have devised a procedure for bacteria by which nonmutant individuals able to grow on the basal medium are allowed to produce colonies on an unsupplemented agar medium. After the locations of these are noted, mutant individuals are "developed" by pouring over the culture plate an agar medium with suitable additions. This method should be applicable to any colonial type microorganism. The use of colonial type mutants of filamentous fungi should make its use practicable in these organisms.

In the case of mutant strains of microorganisms that are capable of growth on a medium on which the original strain fails to grow, the classical enrichment technique of bacteriology can be used. This permits the examination of astronomical numbers of individuals. It has been applied to the measurement of mutation frequencies in bacteria (1), and in the study of back-mutation in *Neurospora* (37, 38). If a method comparable in efficiency with the enrichment technique could be devised for mutants with increased growth factor requirements, progress in chemical genetics could be enormously accelerated.

Genes controlling vitamin synthesis.—Numerous instances of inherited inability of *Neurospora* strains to synthesize specific vitamins of the B group have been reported (5). Tatum & Bell (39) have studied four mutant strains of this fungus that require thiamin or a related compound for growth. Each of these differs from wild type in a single gene. In one strain thiazole synthesis is blocked and in another the mold is unable to couple the thiazole and pyrimidine halves of the thiamin molecule. Two other mutants appear to be of a more complex nature. Monomethylaminoethanol has been shown by Horowitz (40) to be a normal precursor of choline. One mutant of the *Neurospora* that cannot make choline accumulates it while another is able to use it in place of choline. Mitchell & Houlahan (41) have investigated a riboflavinless *Neurospora* mutant strain that grows normally without exogenous

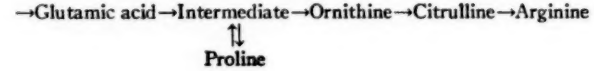
riboflavin at 25° C. and lower temperatures but gives little or no growth in the absence of this vitamin when grown at 28° C. or a higher temperature. Three *Neurospora* mutant strains that require nicotinic acid or a related compound have been reported by Bonner & Beadle (42). When grown under appropriate conditions, one of these mutants accumulates a precursor that can be used by another. This precursor of nicotinic acid is a pyridine compound but has not yet been completely identified. Recently Beadle, Mitchell & Nyc (43) have shown that one of the "nicotinicless" mutants grows when supplied indole, tryptophane, or kynurenine. The study of this mutant strain gives strong support to the hypothesis, based on work with mammals, that nicotinic acid is normally formed from tryptophane. The *Neurospora* evidence suggests that kynurenine is a normal intermediate in this process.

Numerous vitamin-requiring mutants of *Ophiostoma* have been obtained and studied by Fries (35). There are interesting differences in the relative frequencies of various types of mutants in *Neurospora* and *Ophiostoma* but the significance of these is not understood.

In connection with attempts to produce mutant strains of *Penicillium notatum* with increased penicillin-producing abilities, a number of growth-factor mutants were isolated (44). Many of these require specific vitamins for growth. Since this species has no perfect stage, inheritance studies by classical methods cannot be made.

Lindegren & Lindegren (45) have recently made crosses between strains of yeasts (*Saccharomyces*) differing in ability to synthesize certain vitamins of the B group. It is found that ability to synthesize pantothenic acid is differentiated by a single gene from inability to synthesize this vitamin. Similar relations are found between genes and ability to grow without exogenous thiamin, pyridoxin or *p*-aminobenzoic acid.

Biosynthesis of Amino Acids.—Examination of the properties of *Neurospora* and *Penicillium* mutants requiring arginine or a related compound for growth has prompted Bonner (44, 46) to suggest that glutamic acid and proline may be related to ornithine synthesis according to the following scheme:



Six types of mutant strains are known. In each, one of the six reactions indicated in the scheme is assumed to be blocked.

A mutant strain of *Neurospora* that has been difficult to understand in terms of a single blocked reaction is one that requires for growth the amino acids isoleucine and valine. A recent reinvestigation of this mutant by Bonner (47) indicates that the conversion of the keto acid analogue of isoleucine to isoleucine is blocked and that α-keto-β-methyl-*n*-valeric acid accumulated as a result of the interrupted reaction secondarily interferes with a reaction by which the α-ketoisovaleric acid is converted to valine.

A common class of mutants in *Neurospora* (48), *Ophiostoma* (49), *Penicillium* (44), and the bacterium *Escherichia coli* (50, 51, 52) is that in which sulfur metabolism is interferred with in one way or another. In some strains sulfate cannot be reduced to sulfite, in others any of a number of forms of organic sulfur can be used, and in still others, specific sulfur-containing amino acids must be supplied for normal growth. In studying the growth requirements of certain mutant strains in this category in *Neurospora*, Horowitz (48) has recently suggested that *Neurospora* synthesizes methionine as follows:

$$SO_4^{--} \rightarrow SO_3^{--} \rightarrow \text{Cysteine} \rightarrow \text{Cystathionine} \rightarrow \text{Homocysteine} \rightarrow \text{Methionine}$$

Cystathionine has been isolated from the mutant strain that cannot cleave it to form homocysteine. There is little doubt that it is the compound by which sulfur is transferred from a three carbon to a four carbon amino acid.

Other gene-directed syntheses.—Mitchell & Houlahan (53) have analyzed a number of purine-requiring mutant strains of *Neurospora*. Seven genetically distinct types were identified. Inosine is a precursor of adenosine and is itself presumed to be formed from a hypothetical precursor by a gene-controlled reaction. The postulated precursor apparently is not accumulated by the mutant strain that cannot convert it to inosine but is instead irreversibly converted to a purple pigment. Mutants in which purine metabolism is defective are relatively frequent in *Penicillium* (44), and in *Ophiostoma* (54). The studies of Fries on purine-requiring mutants of *Ophiostoma* agree with those of Mitchell & Houlahan in indicating inosine as a precursor of adenosine. A number of pyrimidine-requiring mutants have been found in both *Ophiostoma* (54) and *Neurospora* (5).

Emerson & Cushing (55) and Emerson (56) have reported two mutant strains of *Neurospora*, one that tolerates sulfonamide concentrations that would completely prevent growth of the original wild type, and another that actually requires a sulfonamide for growth. While studies of these strains have not as yet revealed the precise role of sulfonamides in cellular metabolism they seem to indicate quite clearly that these compounds do not act merely to displace *p*-aminobenzoic acid from the site in which it is needed for normal functioning of the cell.

These several examples of gene-directed chemical reactions add substantially to those previously known (5) and serve further to support the view that most of the chemical reactions by which organisms develop and function are under the fairly immediate supervision of genes.

Mechanism of Gene Action

The view that some genes act by controlling enzyme specificities is not new, but experimental evidence supporting it has not been impressive until relatively recently (5). Within the past several years many genetic traits have been studied in which primary gene action appears to be the control of specific chemical reactions. In a few instances such control can be shown to be through the mediation of enzymes. Mitchell & Houlahan (53) have shown that in a specific one-gene mutant form of *Neurospora* the ability to aminate inosine to give rise to adenosine has been lost. McElroy & Mitchell (57) found no detectable difference in the adenosine deaminase of the mutant and its wild type counterpart. It is possible that this deaminase is not the enzyme that catalyzes the reverse reaction, or that inosine amination is not the reaction primarily involved in the mutant strain.

Ginsburg & Kaplan (58) have presented evidence that a skin oxidase present in wild-type mice is deficient in strains homozygous for mutant alleles of the coat color gene *C*.

A consideration of cases in which gene mutations are correlated with specific chemical reactions had led to the formulation of the hypothesis that primary gene action in general lies in directing the synthesis of specific proteins and that genes bear a one-to-one relation to such proteins (5). This would mean that enzyme directing specific chemical reactions should bear such a relation to the genes from which their specificities are copied. Delbrück [discussion fol-

lowing paper by Bonner (46)] has raised the question as to whether the experimental data on which this hypothesis is based have not been automatically selected to favor it. If a gene were to control in a primary way the specificities of say three enzymes, an organism carrying only inactive mutant forms of this gene would fail in three corresponding reactions and, unless three reaction products were supplied to it from an outside source, it would have a small chance of surviving. In an organism like *Neurospora*, mutants of this kind would be likely to be lethal in practice because in general the three necessary reaction products would not be likely to be supplied under the right conditions. Even if such mutants were saved they would be difficult to analyze by the technique routinely used and would be likely to be put aside. There is no doubt that this objection is well taken. On the other hand, if one gene could direct the specificity of more than one enzyme, one might expect occasionally to find single gene mutants with double growth-factor requirements that could not be interpreted on the one-to-one hypothesis. The only clear cut mutant of this type so far analyzed is that requiring both isoleucine and valine for growth. Bonner (47) has shown that a reasonable explanation of it is possible in terms of one blocked reaction and hence one specific enzyme defect. It is clear that additional experimental evidence, possibly different in kind from that now avaibable, is necessary before any decision can be made as to the generality of the one-to-one hypothesis.

The precise manner in which genes transfer their specificities to nongenic proteins remains almost a complete unknown. The answer to this question will almost certainly be essentially the same as the answer to the questions of how specific proteins in general are synthesized and how genes themselves are duplicated. Wrinch (59) has recently addressed herself to this general problem.

Bacterial Genetics

It has already been pointed out that bacterial genetics has only just become a socially acceptable field of interest. The extent to which the genetic viewpoint has affected bacteriology can be appreciated by reading Luria's recent valuable and stimulating review *Recent Advances in Bacterial Genetics* (1). While there are no compelling reasons for doubting that bacteria have genes essentially similar to those of higher organisms or that there exists some precise mechanism for distributing these hereditary units to daughter

cells, there are a number of reasons why bacterial genetics appears superficially different from that of higher plants and animals. In the first place, observations are usually made on very large populations of bacteria, not on individual organisms. Such populations, whether they consist of colonies on a solid medium descended from single cells or suspensions of cells in a liquid medium, are usually of enormous size in terms of number of cells. With gene mutation rates of the same order as found in higher organisms, these populations will almost always be mixtures of diverse types, the proportions of the different types being determined by chance, relative mutation rates, and by selection pressures. Unlike higher multicellular organisms in which the germ line is differentiated early in development of the inividual, any cell in a bacterial population is capable of continuing the line. Finally, although there is now suggestive evidence of some type of fusion process or sexual reproduction in one strain of *Escherichia coli* (60, 61), there has not been known in bacteria a recognizable and experimentally controllable sexual process. Since in classical genetics the gene is a unit of inheritance experimentally defined in terms of sexual reproduction, bacterial genes have had to be investigated by indirect methods. In view of these considerations it is perhaps not remarkable that geneticists and bacteriologists have heretofore had little influence on one another.

The physical basis of inheritance in bacteria.—As a result of the remarkable work of Robinow (62) and others (63), it has become clear that at least certain of the rod-shaped bacteria have well defined chromosome-like structures that go through regular changes during the bacterial division cycle. It seems almost certain that these structures provide the physical basis of orderly gene distribution to daughter cells during fission. In view of these findings, it is not difficult to believe that such structures exist in all bacteria.

Parallelism of genetic phenomena in bacteria and higher organisms.—One of the indirect methods that has been resorted to in the study of bacterial genetics is that of mutation frequencies. If bacteria have genes like higher organisms that undergo random mutation at measureable rates, it should be possible to analyze bacterial populations in terms of such mutation rates. It is difficult to measure mutation rates in bacteria directly because the nature of any given individual must be inferred from the colony (population) it gives rise to, because mutation rates of individual genes are likely

to be so low as to require an inordinate amount of work to measure them, and because the final equilibrium established in a bacterial population is almost always strongly influenced by selection pressures. In *Serratia marcescens*, color variations are frequent. Bunting (64) has shown that if populations of this bacterium are maintained in the logarithmic phase of growth under suitable conditions, there are no selection differentials among different color types and the equilibrium is dependent solely on relative mutation rates. Since these rates are high, they can be measured directly. From the final equilibrium established between red and pink types kept growing logarithmically the relative forward and back mutation rates for the red-to-pink change can be determined. The rate at which the final equilibrium is established is a measure of the absolute rates. The actual rates for the red-to-pink change and the reverse are 10^{-4} and 3×10^{-3} per bacterium per cell generation. The hypothesis that color in this bacterium is gene-determined and that the genes concerned show random mutation at definite rates is clearly consistent with the facts. Braun's analysis (65) of rough-smooth variation in *Brucella abortus* show that the phenomena concerned are capable of being accounted for in terms of gene mutations plus selection pressures.

In particular instances of bacterial variation the question has often arisen as to whether the change observed was a result of an environmentally induced modification or due to spontaneous and random "mutation." To distinguish between these possibilities, Luria & Delbrück (118) have developed the so-called "fluctuation" test. This depends on the assumption that if a given variation is environmentally induced, the proportion of modified cells will be statistically constant from sample to sample whether these samples come from one or several clones. If, on the other hand, the change occurs spontaneously and at random, the frequency of modified cells will vary greatly from clone to clone depending on whether or not a mutation happened to occur early in clonal development. It is also possible by means of the Luria-Delbrück method to estimate mutation rates (1). This clonal grouping method has been applied to phage-resistance in *Escherichia coli* (1), to resistance to penicillin (1), and to sulfonamide in *Staphylococcus* (66), to resistance to radiation sterilization in *E. coli* (67), to histidine independence in *E. coli* (38), and to uracil independence in *Clostridium* (68). In all instances the cellular modifications responsible for these changes

were randomly distributed suggesting that they could have resulted from gene mutation. In all of these studies cultural conditions were purposely such as favor the selection of mutant types.

Witkin (67) has recently reported an interesting mutant type in *Escherichia coli*. As compared with the original, this mutant is much more resistant to sterilization by x-rays or ultraviolet. Its susceptibility to x-ray or ultraviolet induced "gene" mutations, however, remains unchanged (69).

Following the demonstration that genes concerned with the synthesis of vitamins, amino acids and other metabolites could be induced to mutate with x-rays and ultraviolet radiation, similar types of mutants were looked for in bacteria by Roepke *et al.* (119), Gray & Tatum (120), Tatum (70), Burkholder & Giles (71) and others. It is clear that essentially the same metabolic systems exist in *E. coli* as in the fungi *Neurospora* and *Ophiostoma*. For example, Lampen and his co-workers (50, 51, 52) have shown that mutant strains of this bacterium with altered sulfur metabolism parallel closely mutants found in *Neurospora* (48) and in *Ophiostoma* (49). Similarly, the ornithine cycle made evident in *E. coli* through the study of mutant strains (70) is similar to that in *Neurospora*. Roepke (70) has shown that tryptophane synthesis in *E. coli* occurs in a manner similar to that in *Neurospora*. Tatum (70) cites several other examples of similar striking parallels. Since the various syntheses referred to can be shown by direct genetic methods to be gene-controlled in *Neurospora* and *Ophiostoma*, it seems almost inconceivable that the agents which direct the same chemical reactions in bacteria and show the same properties of mutation are not genes with essentially the properties of those of higher organisms.

Delayed appearance of induced mutants.—As already pointed out, phage-susceptible bacteria may spontaneosuly change to phage-resistant types by a gene-mutation-like process. Demerec (72) and Demerec & Latarjet (69) have shown that the frequency of such mutations in *Escherichia coli* can be greatly increased with x-ray or ultraviolet treatment of bacteria. While making quantitative studies of the induction of such mutations, a phenomenon has been observed that may well contribute in an important way to an understanding of the division mechanism in bacteria. This is the phenomenon of the delayed appearance of induced mutations (69). Following raying in either the resting or growing condition, some induced phage-resistant mutants make

their appearance in the treated cell generation, i.e,, without division of the bacteria, but the majority do not show up until one or more divisions have ensued. Only after about thirteen cell generations does the observed mutation rate return to the spontaneous level.

As Demerec & Latarjet (69) suggest, this result might be expected if the rayed bacterial population were heterogeneous with respect to the number of sets of hereditary units, i.e., were irregularly polyploid. Indeed Peshkoff's observations on *Caryophanon latum* (63) suggest that such a situation may exist in this bacterium. On the other hand, the expression of mutant changes may require the exhaustion of some substrate, and the time required for this may vary among individuals (69). Still another possibility is that the mutations may result indirectly through effects on the cytoplasm which may require several generations to disappear. In this connection a most interesting and significant discovery, made by Stone, Wyss & Hass (73), is that mutations for penicillin and streptomycin resistance are induced in *Staphylococcus aureus* by x-raying the medium in which the bacteria are subsequently placed. Here it is evident that the effect is indirect, possibly through the production of mutagenic substances in the medium. If such substances can be produced in the external medium it seems most likely that they would also be produced in the cytoplasm of a rayed cell and would result in delayed mutations such as Demerec & Latarjet have reported (69).

Possibility of sexual phenomena in bacteria.—The existence of some form of sexual reproduction in bacteria has been suggested many times. In fact morphological and experimental evidence have been brought forward in a number of instances [see review by Luria (1) for discussion and references], but to most bacteriologists and others this evidence has not seemed convincing. Sherman & Winge (74) appear to be the first workers to have used a genetic method in attempting to see if bacteria underwent any type of fusion and separation by which characters could be recombined. These experiments, made with the *coli-aerogenes* group and making use of the ability to utilize specific substrates as markers, gave inconclusive results because of instability of the parental lines. A similar approach to the problem was made by Gowen & Lincoln (75) using *Phytomonas stewartii* as test material. No evidence of the occurrence of a heterozygous phase or of recombination of characters was obtained.

Using growth-factor-requiring strains of *E. coli*, Lederberg & Tatum (60, 61) have recently obtained convincing evidence of fusion and segregation. Since the frequency of recombination types is low (of the order of 10^{-7}), it is necessary to use double or multiple mutant types as parents to exclude the possibility of reverse mutation as an explanation of the appearance of types having fewer mutant traits than either parent. The results appear to indicate true segregation. In fact, characters segregate in a nonrandom fashion indicative of a linkage mechanism of some sort (1). These findings are of revolutionary importance for they modify basic concepts regarding the biology of bacteria, particularly mechanisms of evolution, in these relatively simple organisms. Independent confirmation of the Lederberg-Tatum phenomenon is eagerly awaited, not because of any question as to the facts, but because of the great importance of the result and because of a natural question as to how widespread among bacteria the process is. In this connection it is of interest that Lederberg [unpublished result, cited by Luria (1)] and Luria (1) are unable to obtain similar results with another strain of *E. coli*.

Genetics of Viruses

Thirty years ago Troland wrote with remarkable insight about the interrelations of genes, enzymes and the then newly discovered viruses. It is unfortunate that he did not live to learn how prophetic his words were. One of the most fascinating recent developments in genetics is the demonstration by Burnet (1), Luria (121), Delbrück (76, 77), Hershey (78, 79), and others that bacterial viruses are mutable and that their mutation characteristics can best be accounted for on the assumption that an individual virus particle carries several gene-like mutation sites. Related viruses that attack the bacterium *E. coli*, strain B, vary in morphology as determined by electron microscopy, in antigenic properties, in host specificity and in plaque (clear area produced by lysis of bacteria on a Petri dish culture) characteristics. Spontaneous mutations in host specificity and in plaque characters have been observed and studied by several investigators [see Delbrück (76) and Hershey (78) for recent reviews]. Hershey, for example, has shown that the mutation from slow-lysing to rapid-lysing types, accompanied by changes in plaque characters, occurs with a frequency of once per approxi-

mately 10^3 virus duplications. The reverse mutation is much less frequent, occurring about one time per 10^8 duplications.

By the methods that he calls pattern analysis and rate analysis of mutant changes, Hershey (78, 79) has shown that lysis rate (detectable as a plaque character) and host range are independently mutating characters. It is found that the virus designated T2H, which has a certain host range and is a slow lyser, mutates spontaneously and irreversibly to one or another of two types with host ranges different from the original and from each other. All three host range types mutate reversibly to rapid lysers. A mutational change in lysis rate in the original T24 has no effect on the tendency of the virus to give host-range mutations. The rate of one of the two host-range mutations is identical in slow and rapid lysing strains. Essentially similar arguments are used to show that there are two independently mutable host-range factors and at least three independent sites influencing lysis characteristics.

Recombination of characters.—If bacteria are infected with a mixture of viruses not closely related as judged by morphology and serological properties, only one of the two types is multiplied in a given bacterium, a phenomenon called mutual exclusion. The yield of the successful type may be reduced markedly by the unsuccessful competitor [see Delbrück (76) for review]. If, however, two virus strains used in mixed infection are closely related, both may multiply within a single bacterium (76, 78). Delbrück & Bailey (77) observed that if the related types that multiply in a single bacterium differ in lysis characteristics (detectable also as plaque differences), new types may emerge, recombining characters of the virus strains with which the mixed infection was made. Thus if a bacterium is infected with T6*r* and T4r^+ (r and r^+ designate differences in plaque and lysing characteristics; T6 and T4 have different host specificities), the new types of T6r^+ and T4*r* are obtained among the progeny. The data of Delbrück & Bailey do not distinguish between induction of mutation in one phage by another multiplying in the same cell and recombination of virus elements. Hershey (78) has, however, reported experiments in which two viruses involved in mixed infection were strains of T2H differing in three characters and the results of these point to a recombination phenomenon of some sort. Thus, where one infecting virus was *hc*$^+$ *hb*$^+$ *r* and the other *hc hb* r^+, where *hc* and *hb* refer to host specificity

characters and *r* to lysis rate and plaque-type, seven phenotypes were recovered where eight would be predicted with free recombination.

Luria (79a) has recently made a preliminary report on his most remarkable discovery that two phage particles, each inactivated by ultraviolet radiation with respect to ability to multiply when absorbed by different sensitive bacterial cells, can somehow become reactivated when both are absorbed by the same cell. It is suggested by Luria that reactivation involves some type of recombination of gene-like loci that have undergone lethal mutation. X-ray inactivated phages cannot be reactivated in double or multiple infections.

These exciting results strongly suggest that bacterial viruses are structures containing at least several gene-like subunits. With the abundant experimental material available and the most elegant techniques developed by bacterial virus workers, the new field of virus genetics can be expected to develop rapidly.

Chemically Induced Mutations

Nonspecific agents.—During the past twenty-five years or more numerous attempts have been made to induce gene mutations with various chemical agents. Almost all of these have either met with failure or the effects were so slight as to be of doubtful significance. The nucleus of higher plant and animal cells appears to be remarkably well insulated against changes in its chemical environment sufficient to modify genes. The first report of success came from the experiments of Auerbach & Robson, on *Drosophila melanogaster*, in which mustard oil was used. Later, when security regulations were relaxed, it was disclosed that mustard gas (β,β'-dichlorodiethyl sulfide) was much more effective (80). This was administered as a vapor. The incidence of sex-linked lethals was increased from 0.2 per cent in the controls to as high as 24 per cent in the treated series. Subesquent tests of related compounds showed that several of the nitrogen- or sulfur-mustard gases, e.g., β,β'-dichlorodiethylmethylamine, were also active. Subsequent studies by Auerbach & Robson (81, 82, 83) have shown that nonlethal gene mutations, resulting in morphological characters, as well as chromosome aberrations are produced by mustard gases. Like those of x-rays the effects are nonspecific. Treatment of unfertilized eggs gave no increase in mutation frequency in paternal chromosomes subsequently introduced through the fertilizing sperm, suggesting that

the mustard gas effect is directly on the chromosomes. A similar conclusion has been drawn by Muller and by Timoféeff-Ressovsky regarding x-ray effects. It is not obvious how this result is to be reconciled with the observation of Stone, Wyss & Hass (73) that mutations are produced in bacteria by raying the culture medium and subsequently introducing the bacteria.

The effect of mustard gas on chromosome rearrangement has been confirmed by Koller working with the plant *Tradescantia* [cited by Auerbach *et al.* (83)]. Demerec (84) has found that lethal mutations are produced in *Drosophila*, while Horowitz *et al.* (85) have shown that biochemical mutations are produced in *Neurospora*. Tatum has concluded that the nitrogen mustard gas, β,β'-dichlorodiethylmethylamine, induces mutation in *Neurospora* (46) and in *Escherichia coli* (70), although the preliminary reports of this work give no data on mutation frequencies in untreated controls.

The somatic mutation theory of the origin of cancer cells has been considered many times. One of the objections to it has been the lack of mutation-producing effect of carcinogenic chemical substances. Demerec (84) has just recently reported that 1,2,5,6-dibenzanthracene, a known carcinogenic substance, applied to *Drosophila* as an aerosol of a solution in oil increases the incidence of sex-linked lethals by a factor of approximately twenty and that it also produces chromosome breaks. Strong (85a) had previously reported that the carcinogen methylcholanthrene induces coat color and other mutations in mice but because the rigorous genetic control that can be had in *Drosophila* is not possible in mice, there was some basis for skepticism regarding the mouse results. The results of experiments planned to correlate the mutagenic and carcinogenic activities of various compounds will be of great interest for they will provide important evidence for or against the somatic mutation theory of cancer.

Hadorn & Niggli (86) have reported that phenol induces mutations in *Drosophila* in excised ovaries treated with a dilute solution and implanted in untreated females. No confirmation of this reported mutagenic property of phenol has appeared to the reviewer's knowledge.

The experiments of Stone, Wyss & Haas in which mutations were induced in bacteria by x-raying the culture medium have already been mentioned. It has not yet been reported whether the effect in this instance is specific or nonspecific.

Specific agents.—Interest in pneumococcus-transforming principle continues at a high level. McCarty & Avery (87, 88) have made further studies of these high polymers of desoxyribonucleic acid that in the presence of serum or serous fluids have the property of directing mutations of noncapsulated avirulent strains of pneumococcus to types specific with respect to the polysaccharide capsule. It has been shown that the transforming principle from type III organisms is rapidly inactivated by minute amounts of purified desoxyribonuclease under conditions known to favor enzyme activity but not under those known to inhibit it. This evidence still further strengthens the argument that the transforming principle is the nucleic acid polymer and not an impurity. Transforming principles have been isolated from types II and VI pneumococci and, like that for type III, shown to be highly polymerized nucleic acids. A general review of the subject has been prepared by McCarty (89).

Whether the type-specific nucleic acids of pneumococci act by directing gene mutations, or are themselves taken up by the transformed organism to become a part of its gene system remains an unanswered question. In any event it seems clear that they do not serve merely as selection agents for mutations that would have occurred spontaneously. The fluid components have been investigated by McCarty, Taylor & Avery (90), who found that there are at least three of these, viz., the R antibody, a second protein component and a dializable factor.

Boivin, Delaunay, Vendreley & Lehoult (91, 92, 93) have reported evidence favoring the view that mutations in *E. coli* from noncapsulated to capsulated forms can be directed with respect to capsular antigens by a desoxyribonucleic acid fraction. In this case serum factors are not necessary for the transformation to occur but it is essential that the bacteria be in a "susceptible" condition, not yet completely defined experimentally. The evidence that *Escherichia* transforming factors are nucleic acid is not as complete as that for pneumococcus.

Certain of the implications of the directed transformations in pneumococcus and *Escherichia* are obvious. A high degree of biological specificity, formerly thought to be limited to proteins and polysaccharides, can evidently be manifested by polymers of nucleic acid. Whether this specificity lies in chemical makeup of these molecules or in their physical configurations remains to be deter-

mined. As a result of this newly acquired knowledge we are certainly one step closer to an understanding of the gene and the mutation process.

Cytoplasmic Inheritance

There is a tremendous body of experimental evidence indicating that in higher plants and animals the stable hereditary mechanism consists of nuclear genes. On the other hand, every intelligent biologist has appreciated that cytoplasm is an essential medium through which genes act, that it has a certain amount of autonomy, and that it is of great importance in the process of differentiation. During recent years the interest of geneticists has been turned toward the cytoplasm by a number of instances of cytoplasmically inherited traits.

The fact that plastids arise only from preexisting plastid or plastid primordia, and that mutation-like defects in these bodies, not reversible by nuclear genes, may occur and be transmitted for many cell and plant generations has been known for a long time. Rhoades (94) has recently reviewed our knowledge of the interrelation between higher plant plastids and nuclear genes.

The killer character in Paramecium.—Another interesting instance of cytoplasmic inheritance is that involving the so-called killer character in *Paramecium aurelia* studied by Sonneborn and his associates (95, 96). It is found that in a number of varieties of this protozoan there are two kinds of individuals, killers and sensitives. Killers produce a substance in the medium that kills individuals of a sensitive strain in a characteristic way. It has been shown that the killer character is dependent on a cytoplasmic component, called kappa, and a nuclear gene $+^k$. Kappa can only be multiplied if allele $+^k$ is present in the nuclei but it cannot be initiated by this allele; that is, some kappa must be present for more to be produced. If allele $+^k$ is replaced by k, an alternate form of the same gene, kappa is no longer multiplied. Preer (97) and Sonneborn (95, 96) have shown that in $+^k$ animals containing kappa, the multiplication of kappa need not keep pace with multiplication of the entire organism. Thus in variety 2 Preer finds that well-fed organisms kept under favorable conditions increase faster than kappa can multiply. By a series of ingenious experiments Preer was able to show that there are about 250 kappa particles in killer animals, that if this number is reduced below a threshold the animal be-

comes a sensitive that can revert to a killer if its division rate is reduced, and that if a high division rate is maintained for a sufficient time, some animals run out of kappa entirely and become permanent sensitives. He was able to show that an individual with only a single kappa particle is capable of reverting to a sensitive. Working with variety 4, Sonneborn has confirmed Preer's findings. Killers of this variety cannot be made to outgrow their kappa by optimal feeding but can be made to do so by growing them at a temperature of 38.5° C. If maintained for three to four days, this temperature is lethal, but if killers are exposed to it for shorter times, kappa is reduced in amount or eliminated. Thus after twelve hours killers become sensitives that can be reversed while after thirty-six hours they become permanently sensitive. Kappa can be transferred to $+^k$ $+^k$ sensitive animal through the cytoplasmic bridge that may be formed during conjugation of the $+^k$ $+^k$ sensitive (no kappa) animal with $+^k+^k$ (with kappa) animal. In this way Sonneborn has succeeded in transferring as few as two to four kappa particles. These leave the animal that received them sensitive but capable of becoming a killer when the fission rate drops at autogamy or during old age sufficiently to allow kappa multiplication to exceed cell fission by six or seven times—that is, when the number of kappa particles is increased to approximately 256 (2^8).

It is found by Sonneborn (95, 96) that all characters investigated in the B group of varieties, to which variety 4 belongs, involve a kappa-like cytoplasmic determinant. These characters include the killer character, antigenic properties and mating type. There is no evidence of comparable cytoplasmic units for similar characters in group A varieties.

Other instances of cytoplasmic inheritance.—Sonneborn (96) and others have found that resistance of a strain of *Paramecium aurelia* to antiserum directed against the same strain may be induced by treatment of the susceptible animals with the antiserum. Such resistance is known to be transmitted through many vegetative fissions, but not through sexual reproductions. Kimball (98) has observed that resistance is also induced by treatment with trypsin. It is supposed that susceptibility is dependent on an antigen which may be temporarily depleted through combination with antibodies or by tryptic digestion of the antigen itself or a precursor of it. Whatever is destroyed by trypsin is supposed by Kimball to be formed autocatalytically for it would otherwise be expected to

reappear after very few fissions. It is interesting to note that crosses between strains susceptible to antiserum against stock 60, variety 1, and others resistant to such an antiserum show the antigen concerned to be gene-controlled.

L'Heritier and his associates (99, 100) have for some years concerned themselves with the inheritance of susceptibility to carbon dioxide in *Drosophila melanogaster*. This trait is transmitted from generation to generation independently of chromosomes and apparently through the cytoplasm. It is much more effectively carried through the egg than through the sperm as would be expected if it were a cytoplasmic entity. Its sensitivity may be abolished temporarily or permanently by subjecting affected flies to either high or low temperatures and can be transmitted from an affected animal to a resistant one through ovary or brain transplants or through transfer of cell-free lymph [work cited by Ephrussi in discussion of paper by Sonneborn (95)]. The carbon dioxide-susceptibility character is apparently subject to an interpretation similar to that advanced for the killer character in *Paramecium* (100). Other instances of supposed cytoplasmic inheritance are those in wheat and oat rusts recently summarized by Johnson (101). These involve the transmission of pathogenic characteristics.

Mampell (102) has continued his studies on a strain of *Drosophila pseudoobscura* showing a high spontaneous mutation rate. He postulates the existence of both a mutator gene and a cytoplasmic component that can be transferred by contact from one strain to another or even from *Drosophila pseudoobscura* to *Drosophila melanogaster*. The situation is not yet well understood and the evidence for the self-reproducing cytoplasmic factor postulated by Mampell is not entirely convincing.

It is, I believe, cause for reflection that none of the instances in which cytoplasmic inheritance is firmly established is a self-duplicating gene-like structure involved that cannot reasonably be supposed to be gene-dependent. Thus, while Sonneborn's kappa is certainly self-duplicating in the sense that some must be present before more can be formed, it cannot continue to be elaborated in the absence of the $+^k$ allele of a specific gene. It is true that such gene-dependence has not always been demonstrated, but as Sonneborn (96) has pointed out this may mean merely that the active forms of all essential genes are present in all strains investigated. An alleged case of cytoplasmic transmission that would seem to the

reviewer to require a basic change in our conceptions of genic control is that first reported by Lindegren, Spiegelman & Lindegren (103, 104) in yeasts. Here, it is claimed, there exists an enzyme melibiase that in the presence of the substrate melibiose is capable of indefinite self-duplication in the absence of the gene that initiates it. It is true that the supposed self-duplicating cytoplasmic entity may be an enzyme precursor rather than the enzyme itself but it remains that we have here a postulated cytoplasmic unit that is capable of permanently substituting for a gene. There has been a great deal of discussion of this situation (105). In fact an elaborate theory (the so-called cytogene theory) has been developed as a result of the reported facts (106, 107). It appears from a recent publication of Lindegren & Lindegren (107) that the critical experiments on which the self-duplicating enzyme hypothesis was based cannot be repeated. The cytogene theory has apparently been abandoned (45). Evidently a final appraisal of the situation in yeast must await the straightening out of the basic experimental facts.

Symbiosis and the origin of cytoplasmic hereditary units.—Altenburg (108) has suggested that cytoplasmic factors like kappa in *Paramecium* might well have arisen from symbionts such as the green algae found in *Paramecium bursaria*. While, as Sonneborn (96) has pointed out, strong arguments can be advanced against such an interpretation in the case of the killer character, it is not easy to rule out the symbiont hypothesis completely. In fact, on logical grounds one would expect in certain cases the genes of an intracellular symbiont to take over the functions of one or more genes of the host organism. This has apparently occurred in the cockroaches where bacteria-like organisms live symbiotically in the fat body cells of the insect. The "bacteroids" have not been cultivated in the absence of living cells nor can the host live if the symbionts are abolished by penicillin treatment (109). Apparently each of the symbiotic partners has become irreversibly dependent, presumably through a process of complementary gene mutation. The cockroach is dependent on genes of the bacteria and vice versa. The degenerate bacteria are transmitted cytoplasmically through the egg of the insect. If the intracellular symbiont were to retrogress somewhat further, affect the host in a nonvital manner and to be less obviously descended from a bacterium, one would certainly conclude that it constituted a self-duplicating cytoplasmic hereditary factor.

How general is cytoplasmic inheritance?—However gene-like cytoplasmic hereditary units may arise, it does not seem likely that they are of widespread occurrence. If self-duplicating enzymes or enzyme presursors of the Spiegelman-Lindegren variety were the rule we would not expect experimentally to find the numerous biochemical mutants that have been demonstrated in *Neurospora* and *Ophiostoma* and which differ in nuclear genes from their synthetically more complete counterparts. Furthermore we should expect to find many deficiency mutants that differ from the original type only in a cytoplasmic component. It seems highly probable, as Sonneborn (96) and others have pointed out, that cytoplasmic substitutes for nuclear genes would become established only under special circumstances. The ciliates in which a division of labor between two kinds of nuclei has become established might well constitute just such a special case. The almost universal distribution among existing organisms of the nuclear gene mechanism of heredity is good evidence that it represents the most effective machinery that mutation and natural selection have so far succeeded in devising.

Plasmagenes in another sense.—It seems entirely possible that many nuclear genes may direct the synthesis of elements capable of multiplication in the cytoplasm. As Wright (110), Burnet (111), Spiegelman (104), Boivin & Vendrely (112), and others have pointed out, this assumption is not unreasonable on the basis of our knowledge of phenomena such as cellular differentiation and the multiplication of adaptive enzymes. Wright (110) has indicated how such gene-initiated self-duplicating cytoplasmic elements, which have been called plasmagenes, might, under the influence of local environmental conditions in a developing organism, become systematically modified without losing the ability to multiply. An orderly succession of such modifications might well underlie the process of differentiation. Plasmagenes in this sense are not cytoplasmic substitutes for nuclear genes but rather are conplementary to them.

Evolutionary Considerations

The Horowitz hypothesis (113) which has to do with the evolutionary history of systems of biosynthetic reactions was mentioned in a previous volume of this series (2). There are two recent contributions that have a bearing on this general question. One is the observation by Monod (114) that a methionine-requiring

Aerobacter mutant grows appreciably faster on a methionine-containing medium than does the wild type strain from which it was derived. One cannot, of course, generalize from a single instance of this kind, but it would be most significant from the standpoint of evolution if it were frequently the case that loss mutants were more successful than their synthetically more complete counterparts in an environment rich in the product of the reaction blocked in the mutant. It is of course a well known fact, as has been pointed out especially by Lwoff (115) and by Knight (115a), that evolutionary specialization through loss of synthetic ability has occurred in many groups of organisms. It seems probable that genes that become inactive in this process are available for mutations that add new synthetic reactions and thus serve to make possible positive evolution (116).

Houlahan & Mitchell (117) have reported a situation in *Neurospora* that may have an important bearing on the question of positive evolution. It is found that the pyrimidine requirement of a mutant strain can be abolished through mutation of a gene that is genetically independent of the one involved in the original mutant change from wild type. Such "suppressors" have been known for a number of mutant traits in *Drosophila* but this is one of the clearest so far as knowing the affected system of synthesis is concerned. If the normal function of one gene can be taken over by a mutant form of another, it seems possible that the direction of an entirely new reaction could be taken over by an unneeded gene in essentially the same manner.

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DEVELOPMENTAL PHYSIOLOGY[1]

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The problem confronting the reviewer is, as usual, how to present the field in the space allowed. No apologies are offered for materials not included, for with the work which is now coming from abroad, there is less opportunity than usual to get a bird's eye view of the field. Fortunately many of the laboratories abroad have summarized their work in such succinct form that their main lines of effort are apparent. It is with considerable appreciation that their attainments during the war period can be referred to here. Since these represent laboratory reports they will be given here in toto as such instead of being treated separately under different headings.

The first of these gives the chief lines pursued by Brachet & Jeener (1) introducing micromethods for detection of thymonucleic and ribonucleic acids in tissues by analyzing the glucidic radicals of these acids. They have hydrolyzed ribonucleic acid by using ribonuclease and have used Feulgen's reaction for detection of thymonucleic acid. Research on the localization and role of nucleic acids in the cell and in the embryo has been continued: where ribonucleic acid is abundant the cell synthesizes protein. The physical properties of nucleic acids and nucleoproteins were studied: (*a*) action of varied concentrations of nucleohistone in saline solutions with a comparison of the concentrations occurring in living cells, and (*b*) properties or ribonucleic proteins where the conclusion is drawn that the cytoplasmic granules are the synthetic agents for forming specific cell proteins.

Thymonucleic and ribonucleic acids can change into one another during the course of different cellular actions. Synthesis of ribonucleic acid is possible in yeast where the basophilic granules increase with addition of phosphate. In this case nucleic acids combine to form metaphosphoric acids, the reaction being indicated by metachomia.

Van Campenhout (2) has given a brief summary of the work

[1] This review covers the period from July, 1946 to August, 1947.

done in Louvain. He has studied the development of the cranial nerves in pig embryos and has demonstrated the important role of placodes in the development of the cranial nerves in pig, chick and duck embryos. The ganglion crests of the rhombencephalon are not necessary for the differentiation of the placodes. Cells derived from the villous duodenal epithelium assume the characteristics of neuroblastic elements. De Muylder has described the intrarenal system in the mouse. The origin of the entire nervous system has been studied in chick embryos by chorioallantoic grafts.

Dalcq (3) has reviewed the contributions of the Dutch investigators to brain morphogenesis in Amphibians. Carefully controlled x-radiation of axolotl embryos during pregastrular stages gives true microcephaly without cyclopia or monorhinia; when exposed at neurula stages microphthalmia does not occur but there is a shortening of the cerebral parts (Trampusch). Nieuwkoop grafted dorsal lip into ventral marginal zone of another gastrula. He secured various degrees of reduction in the anterior parts of the brain only. Dalcq has performed a latitudinal translocation in which the animal pole of *Diacoglossus* is rotated 180° and then replaced upon the vegetal material. A double embryo results. On the basis of these results and unpublished work by Damas and Gallera, Dalcq concludes that the neural plate results from the combined action of the notochordal part of the archenteric roof, the parachordal mesoderm (with oto-evocators) and the prechordal plate. Symmetrical relations in the forebrain are the result of a high level of induction; bilaterality is intrinsic to induced neural tissue and is governed by the law of size limitations which Dalcq feels seem to have general application in animal organization.

Woerdeman & Raven (4) review the work at Amsterdam and Utrecht. Woerdeman's work deals mostly with determination and induction, Trampusch with induction and the x-radiation experiments discussed by Dalcq (3). There are also studies on the development of teeth in urodeles and, by van Deth, pro- and mesonephric development in axolotl embryos. The biochemical side is represented by Ten Cate's measurement of respiration and associated studies along with studies on the influence of trivalent arsenic on amphibian eggs and carcinogenic carbohydrates on the development of amphibian larvae. In addition there is a study given by Damstra on the use of trypsin in decapsulation of anuran eggs. In the avian field, van Deth studied the developmental potencies of

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primary gonocytes and Huybers the development of the gonads and their ducts after the grafting of another gonad.

At Utrecht the research has centered around the development of *Limnaea stagnalis L.* The studies include oviposition, sperm and egg paths and egg mass formation, oögenesis, cytoplasmic processes in the uncleaved egg, physical changes along with centrifugation experiments and the action of lithium and sodium sulphocyanide. There are also studies in amphibian experimentation on the determination of the neural crest and a remarkable study by Nieuwkoop on the origin of primary germ cells and genital ridges.

Experimental Morphology

Tubifex.—Gaiser (5) studied the effect of carefully graduated ultraviolet radiation upon maturation and early cleavage division of *Tubifex* comparing susceptibility with that of the relatively yolk-free *Ascaris* egg. The first segmentation metaphase was found to be by far the least sensitive stage. The curve of degree of injury is not exponential but is an ogive.

Lehmann *et al.* (6) have conducted a series of experiments to determine the effects of various substances upon mitosis in *Tubifex.* 1, 4 benzoquinone and 1, 4 naphthoquinone are inhibitive antimitotics blocking mitosis at the phase of maximum plasma movements in the ana- and telophases. The destructive antimitotics act upon the nuclear apparatus by dissolution, colchicine upon the inter- and prophase nucleus, while stilbestrol and 9, 10 phenanthrenquinone are effective chiefly upon the achromatic apparatus.

Echinoderms.—Harvey (7) has succeeded in separating the egg of *Arbacia* into quarters by centrifugation. She secures a clear quarter which contains the oil cap, nucleus and the greater bulk of the clear material or matrix. This quarter, if fertilized some time after centrifugation, will develop into a perfect small pluteus. She concludes that the important cytoplasmic material is the matrix or ground substance, not the egg granules.

Four specific interacting substances have been derived [Tyler (8, 9, 10)]: fertilizin from eggs, antifertilizin from sperm, egg membrane lysin from sperm and antifertilizin from eggs. The antifertilizin from sperm is a protein of comparatively low molecular weight, isoelectric point at pH 3. By preparing antisera in rabbits it was found that fertilizin and both antifertilizins were active antigens producing antibodies that gave good precipitation reac-

tions. By photo-oxidation the antibodies can be converted into a non agglutinating form which is termed "univalent." Extractions in dilute acid sea water pH 3.5 to 2.8 show swelling in the head region between the acrosome and midpiece which is concluded to be the region from which the antifertilizin is derived.

Mollusca.—Raven (11) and his coworkers are developing the study of normal development of the mosaic egg of *Limnaea.* Bretschneider [see (4)] has investigated the topography of the genital tract showing the pathways of egg and sperm and the rate of formation of the egg mass.

The egg-laying stimulus has also been investigated (4). Temperature is important, as well as O_2 produced specifically by *Hydrocharis;* at 17° to 18°C. 50 per cent of the snails will lay in five hours with the first egg mass at two hours; at 21° to 26°C. egg laying begins at two hours with 70 per cent of the snails reacting.

Experiments in which *Limnaea* eggs were exposed to the action of lithium chloride are also reported by Raven (12). Long exposure to lithium chloride is harmful but lithium in tap water can serve as a stimulant to development; head anomalies resulted when the eggs were returned to tap water in actual mitotic phase after short exposures. The action of lithium on *Limnaea* is apparently founded on the selective influence on the animal pole or on the processes which concentrate this material there.

Teleost.—Oppenheimer (13) has reviewed the literature dealing with Teleost organization. In experiments on *Carassius,* Tung, Chang & Tung (14) found that the blastodisc can be removed at the eight-celled stage and that embryos will be formed. Hyperblastulae are formed in earlier latitudinal separations in which about half the yolk is included. Devillers (15) isolated blastoderms of *Esox lucius* at the blastula stage and cultivated them in 3 X Holtfreter's solution.

An unusual case of twinning in *Fundulus* is reported by Oppenheimer (16). The components were arranged in tandem with their longitudinal axis in the same meridian. She suggests a division of the shield or involution along a single axis in two phases separated by time as a cause for this arrangement.

Amphibian.—Taylor & Kollros (17) have divided the larval and metamorphic periods of *Rana pipiens* into twenty-five morphologically distinct stages. Data are given for size at each stage, intervals between stages, changes in pigmentation and behavior.

Embryonic cellular behavior.—Holtfreter (18) has added a series of comprehensive studies upon isolated embryonic cells. These are significant because of their conceptual approach. Holtfreter has in mind the similarity between isolated early embryonic cells and *Amoeba.* In isotonic salt solution the cells form pseudopodia and move demonstrating an inherent monaxial polarity. Movements are initiated by the cell membrane which undergoes annular constrictions. He assigns a causal role to alternate states of hydration in the plasmalemmal phosphatides. Cellular division is regarded as resulting from annular constriction of the plasmalemma. The second paper (19) deals with changes in structure and kinetics of differentiating cells. Here Holtfreter deals with cell species studied in isolation after removal from the gastrula of *Triturus* and cultured in salt solution for five days. The monaxial polarity of isolated myoblasts is evident in the gastrula. When an ectoderm cell is induced to form a neuroblast it changes to a cylindrical body instead of spreading centrifugally.

Interfacial tension (20) is responsible for the aggregations which isolated embryonic cells establish. In a study of cytolysis (21) at sublethal levels it was found that neuralization can be caused by any mildly cytolyzing agent while anticytolytic agents bring about epidermization.

Invagination and organizer action.—Lewis (22), after studying the various invaginating structures in the amphibian embryo, has constructed a mechanical model which illustrates the conditions of invagination as he interprets them.

Child (23) has again recalled the evidence from forms other than amphibians which bear upon the problems of organization and particularly upon the organizer concept. He points out the dangers of too great a tendency for generalizations drawn from one type of embryo.

Lehmann (24, 25, 26) has discussed some of the problems of organization in the formation of ventral organs. Further consideration of these problems appears in papers by Nicholas (27, 28). Lehmann (25) reviews the whole subject and on the basis of previous work draws up an anlagen pattern which includes endodermal and lateral as well as axial structures. It is not, however, correct to state that the organizer fixes the capacity of germinal parts other than ectodium.

When the egg is dissected either uncleaved or in the two-celled

stage, Lehmann found that he could identify the gray crescent by the allocation of materials which he interprets as a presegmentation localization. In another paper (26) he distinguishes two specific parts of the archenteron which induce the anterior part of the brain and the nervous system between the otic capsules and also a third which induces the cord.

While Lehmann found a marginal plasma in the unsegmented egg, Pasteels (29) who reinvestigated this point found no such structure but comes to the conclusion that the marginal zone constitutes an integral part of the animal pole region, being in direct contact with the upper layer of large yolk granules in the vegetative part.

Centrifugation of blastula (30) or gastrula in Amphibia causes the appearance in ectodermal regions of ectodermal and mesodermal structures. After transplanting ectoderm from an egg that has been centrifuged, a secondary embryo may be formed without any contact with the normal organizer region. Such grafts contain a high concentration of ribonucleic acid which is thought to be produced by the cellular trauma caused by centrifugation. In a second report on centrifuged tissues (31) Pasteels notes that the explants differentiate less frequently than if the material were left *in situ*. When transplanted, secondary embryos tend to lie parallel to the primary embryonic axis and implants of centrifugal ectoderm can induce modifications of normal structures. He states, "*la thèse des substances inductrices spécifiques doit être abandonnee.*"

Brachet (32) reports that the nucleoproteins, nucleic acid and certain of their derivatives are active evocators. The content of ribonucleic acid decreases during the course of invagination and simultaneously increases in the presumptive nervous system.

Germ Cells.—The problem of origin of the germ cells in Urodeles is the subject of an exceedingly interesting paper by Nieuwkoop (33). The endoderm was removed at a late neurula stage and the endoderm free ectoderm-mesoderm sheet allowed to develop. The results are striking beyond their interest in the germ cell problem. The axial body parts develop, the splanchnopleure does not differentiate as smooth muscle but becomes somatopleure and in addition forms a pair of limbs. Heart is not formed. The germ cells are missing and his conclusion is that the germ cells arise in the lateral plate.

In triploid axolotls, Humphrey & Frankhauser (34) have

studied the development and functional capacity of the ovaries. Up to three months they differ little from the diploids but many oöcytes degenerate at the beginning of the growth phase. The hypophysial reactions are normal; degeneration is not due to the chromosomal sex-determining mechanism but to the presence of a third set of chromosomes when the oöcyte nucleus is suspending meiosis in favor of metabolic activity.

Fertile eggs were secured from a two year old tetraploid female axolotl which was mated with a diploid mate (35). Viability of the eggs was low, about one-half lived to stage forty; the deficiencies were in the main vascular. Sixteen were still alive at two months. Chromosome numbers showed only two larvae which showed the expected triploid number. The high number of unbalanced chromosome complements explains the low viability. This is the first breeding test of tetraploid vertebrates.

In hybridization studies Moore (36) has studied female *R. pipiens* × male *R. sylvatica* and finds that the majority of the embryos are arrested at the gastrula stage. Invagination is restricted to dorsal lip region only, resulting in a few axial structures. The structures anterior to the neural tube are abnormally placed. When the gastrula ectoderm of such hybrids is removed and given the proper stimulus through completely invaginated tissues, it possesses competence for neural formation (37).

In hybridizing *Triturus cristatus* and *T. marmoratus* the females are generally fertile, the males entirely sterile (38). A comparison of F_1 hybrids and double back cross newts suggests that the sterility of the male hybrids depends on the interaction of a number of genes.

Neural crest.—De Beer (39) has reviewed much of the experimental work on the neural crest. By fertilizing enucleated *Triturus rivularis* eggs with *T. torosus* sperm, Dalton (40) has secured neural crest material which, when transplanted, gives rise to melanoblasts. There is a clear dissociation of nuclear and cytoplasmic effects in development.

Niu (41) divided the neural fold into five transverse segments and studied the pigment cells which developed from each in saline solution or coelomic fluid. The anterior segment gives a low percentage of pigment cells when compared with the posterior trunk fold which gives nearly 100 per cent; there are practically no pigment cells in the short caudal fold. He suggests that cells which

normally would give rise to other structures may be transformed into pigment cells.

Hörstadius & Sellman (42) have published a monograph giving in detail the contributions of the neural crest to the cartilaginous head skeleton of Urodeles.

Chick development.—In a series of studies on the explanted blastoderm Spratt (43, 44) has utilized carbon particle markings. By using fixed reference points on the plasma clot he has obtained measurements of the direction, extent and rate of cell movements. The right and left posterior fourths of the pellucid area of the prestreak blastoderm converge postero-medially and invaginate through the developing streak as mesoderm. Marked cells at the anterior end of the short streak remain in position while the streak differentiates anteriorly out of the epiblast anterior to the marked cells, accounting for 20 per cent of the definite streak length. Growth throughout the posterior half of the streak accounts for its future elongation. Later, the primitive streak shows an actual regression and shortening. The region of cell growth is found just anterior to the node. Marked node cells become the "tail bud" cells which act in the formation of the embryo behind the twenty-seven somite level. Some movements of the epiblast are relatively autonomous while others are relatively dependent. Rudnick (45) has reviewed the work on the delineation of the prospective areas and differentiation potencies in the chick blastoderm.

Biochemistry of the Embryo

An exceedingly brief summary of chemical determination in ascidians, frogs, salamanders, sea urchins, perch, common viper and guinea pig is given by Kühn (46).

An analysis of the egg of *Limnaea* (47) shows that about 5 per cent of the egg volume is fat as saturated fatty acids with some unsaturated. Lipoids are found around and between the granules at top of centrifuged egg. Glycogen is present in diffuse form; it shows a slight increase in the first half of oögenesis, greater in the second. No thymonucleic acid is present during oögenesis. Old oögonia and young oöcytes have chromosomal thymonucleic acid; it is then lost and reappears after tetrad formation.

Young oöcytes have a high concentration of ribonucleic acid; this declines during development. It is located in the periphery of the cell in normal ova; in the centrifuged it is in the hyaloplasm.

It is found in the basophilic part of the nucleolus. Reduced glutathione is first found in the nucleolus from which it is emitted to the nucleoplasm and also in the cytoplasm.

Phenolase is found first near the Golgi apparatus, then in the nuclear region and in young oöcytes throughout the whole periphery of the egg. After centrifugation it forms a broad band in the lower part of the hyaloplasm on the boundary of the proteid yolk.

Physically (48) the egg of *Limnaea* is isotonic with 0.09 to 0.10 molar solutions of nonelectrolytes at the time of laying. The permeability constant for distilled water gives $P = 1.13$ to 2.14×10^{-7}. Tension at the surface has been determined and a graph is given showing the changes during development.

A study (49) of the inorganic constituents of developing salmon eggs has been made. Amounts of sodium, calcium, potassium, magnesium, chlorine, inorganic phosphorus and water have been determined. The embryo shows almost complete transformation of the yolk content since the initial weight of the yolk is 118 mg.; the weight of the embryo after consumption of yolk is 110 mg.

Boell (50) has shown that amphibian dorsal lip tissue at gastrulation is characterized by a relatively intense metabolism. Boell has been able to show that enzyme growth constants are distinctly different. Embryos reared in diisopropylfluorophosphate continue to synthesize cholinesterase at about the same rates as the controls. In contrast to the discreteness of the biochemical method given above, histochemical investigations show much less regional difference [Holtfreter (51)].

Glycogen.—Lindberg (52) describes the result of determination of free and bound glycogen in sea urchin eggs before and after fertilization and after freezing. Elftman & Copenhaver (53) studied the localization of alkaline and acid phosphatase and glycogen in *Amblystoma* embryos ranging from late blastular to feeding stages. In late blastula, alkaline phosphatase is present in the yolk granules of both animal and vegetal poles; acid phosphatase is more abundant in the vegetal pole, glycogen in the animal pole.

In the rat uterus, Boettiger (54) has studied the deposition of glycogen, which reaches maximum level in proestrus under control of estrogen which acts even in ovariectomized rats.

Respiration.—The effect of cyanide on oxygen consumption and cleavage of the sea urchin egg has been studied by Robbie (55) using methods for control of hydrogen cyanide tension. The un-

fertilized egg is almost completely inhibited by 10^{-4} *M* hydrogen cyanide. Residual respiration after four hours is 43 per cent of the control value. Residual oxygen consumption in both 10^{-4} and 10^{-3} *M* hydrogen cyanide is increased by raising the oxygen tension to 100 per cent and is decreased by lowering to 4 per cent. Fertilized eggs are lowered 82 per cent by 10^{-4} *M* hydrogen cyanide.

Barth (56) has studied the effects of reduced oxygen tension on the frog's egg in order to discover something about anaerobic mechanisms acting in release of the organizer. Lactic acid is produced in linear relation for six hours then declines. The bound carbon dioxide of the egg is released. Some base is produced along with the lactic acid which prevents it from releasing carbon dioxide completely. The true RQ is greater than unity (*ca.* 1.5) at the low oxygen tensions.

When respiration of whole embryos is compared with embryonic brei, the former is low, this situation reversing at stage 17 [Spiegelman & Steinbach (57)]. Cyanide depresses the respiration of both eggs and brei; azide depresses oxygen consumption and development of intact embryos, but has little effect on the brei.

Hexenolactone inhibits frog development in concentrations as low as 5×10^{-5} M [Briggs (58)]. Sensitivity is greatest at the beginning and decreases through blastula and gastrula; it increases in the post neurula. Cleavage of the vegetal hemisphere is inhibited, nuclear cleavage takes place without cytoplasmic division. After gastrulation the decrease continues but the rates are different, the haploid being much more sensitive.

Connon (59) has determined the respiration rate on three species of *Triturus* and also on hybrids of *T. torosus* ♀ × *T. granulosus* ♂ and *T. rivularis* ♀ × *T. torosus* ♂. In the early stages of development the hybrid embryos follow the maternal species closely in both developmental and respiratory rate.

In a study of the inhibitory action of naphthoquinones (SN-5949) on cleavage and respiration in the eggs of *Arbacia*, Anfinson (60) finds that at 7.4×10^{-7} M respiration of both fertilized and unfertilized eggs was inhibited 70 per cent and 50 per cent respectively. At less than the above molar concentration respiration was stimulated. Decreased pH caused an increase in respiratory inhibition over the range 6.5 to 8.1.

Flexner & Flexner (61) have continued their studies on bio-

chemical differentiation in investigating formation of succinic dehydrogenase and succin-oxidase in the cerebral cortex of the fetal pig.

Metabolism.—The nitrogen metabolism of *Rana pipiens* has been analyzed by Gregg & Ballentine (62). Little combustion of protein occurs during the development of the embryo. The average total nitrogen of one jelly-free embryo is 162 micrograms, 40 micrograms of which are in the protein fraction extractable with 0.65 per cent sodium chloride in .01 M phosphate buffer at pH 7.4; four micrograms in the total non-protein fraction and three micrograms in the total lipid fraction. Total nitrogen decreases at first and increases at stage 19; total nonprotein nitrogen decreases 12 per cent during cleavage and gastrulation, then rises to 125 per cent of the original by hatching. During development less than 8 per cent of the total non protein nitrogen is accounted for by the sum of free ammonia, urea ammonia, glutamine ammonia and other ammonia released by acid hydrolysis.

Barth (63) has investigated the respiratory rate in hybrid eggs [cf. (36, 37)]. During gastrulation a new respiration develops both in the normals and in the hybrids establishing an RQ of 0.87. Development is limited due to a deficiency in some substance necessary for oxidation of all of the substrates.

Phosphatase.—Acid phosphomonoesterase rises to a maximum at six days in homogenates of chick embryos [Moog (64)]. Alkaline phosphomonoesterase activity rises between two and four days, declines from four to six days and then rises to a second maximum at ten days.

Moog & Steinbach (65) have examined the granule content of chick embryo homogenates sedimented at 21,000 × *g.* for the distribution of alkaline and acid phosphomonoesterase. The first granule fraction contains the largest part of the nitrogen as well as alkaline and acid phosphatase at ten days of incubation. Calcium activates alkaline phosphatase in granules and in supernatant in approximately equal amounts.

In frogs' eggs which have been freed from yolk by centrifugation at 500 × *g.*, Moog (66) finds the alkaline phosphomonoesterase unchanged to the end of gastrulation; it doubles by the tail bud stage and increases tenfold between stages eighteen and twenty-five.

Adenylpyrophosphatase (67) rises threefold in terms of total ni-

trogen in chick embryos from three to twelve days of incubation. In the brain it reaches its maximum seven days after hatching; in skeletal muscle the peak comes at hatching then declines; in heart the peak comes at sixteen days incubation, declines at hatching and increases to adult level.

Effects produced by nitrogen mustard.—Developmental inhibitions [Gillette & Bodenstein (68)] and ectodermal effects [Bodenstein (69)] have been presented showing the specificity of nitrogen mustard upon the mitotic process without retarding histological differentiation.

Nervous System

Cell distribution and behavior.—Sensory ganglion cell bodies [Humphrey (70)] were found in the central canal of the spinal cord in eight out of ten human embryos from 5 to 37 mm. in C-R length but not in older specimens. She suggests that these cells have a neural crest origin. The behavior and movement of human foetal brain cells have been studied in cultures by Hogue (72, 73). The cells were cultured as long as 142 days and their movements, migrations and relationships noted.

Sprague (71) has studied the distribution of axons from the motor cell group in the spinal cords of sheep from twenty-one to thirty-four days of age. Groupings of the motor cells are present from the earliest stages of neurofibrillar development and these groups do not differentiate from a common cell mass. Each group contributes to both rami.

By embryonic operations, Piatt (74) tested for possible hypo- and hyperplasia in the mesencephalic V nucleus of *Amblystoma.* When the mandibular arch is extirpated there is a consistent hypoplasia with an average reduction of 41.2 per cent. When an *A. tigrinum* arch is substituted for the *A. punctatum* mandible he secured a hyperplasia of 16.6 per cent.

Power (75) has been able to show that similar morphogenetic reactions occur in *Drosophila.* Mutants showing reduction in the compound eye were employed. The architecture of the antennal glomerulus is not changed but its volume changes linearly with the volume of the eye. With complete absence of the eye there is a hypoplasia of 27 per cent in the antennal glomeruli. This relationship is unilateral.

Mauthner's cell.—Greene (76) has worked out the differentiation of this unique cell and correlated it with Harrison's stages

and Coghill's motility phases. Its dendritic field is synchronized with the total reaction pattern and is elaborated as the acoustico lateralis inflow is perfected. Extirpation of the synaptic primary sensory neurones depletes the lateral dendritic field.

In a study of the factors controlling the differentiation of Mauthner's cell, Piatt (77) performed extirpation and transplantation experiments on the associated roots and ganglia. Differentiation of Mauthner's cell is dynamically related to its juxtaposition to the vestibular and lateral line nerve roots and tracts. The VIIth and Xth lateral line nerve roots may also be effective (78).

Detwiler (79) tested the locomotor capacity of larval *Amblystoma* lacking Mauthner's neuron or the ear, using a miniature race track by which he could calibrate the distance traversed. In younger stages the larvae lacking the ear travel the shortest distance; in later stages they equal normals. Those lacking Mauthner's neuron were less active than the normals. Detwiler (80) replaced the midbrain with the cephalic portion of the cord, reversed the midbrain completely and also unilaterally; then tested capacity for locomotion. At stages forty to forty-one the mesencephalon starts to control locomotion. There is little effect on locomotor activity after excision of forebrain while it declines after stage forty-one in animals lacking midbrain (81).

By means of tantalum foil blocks Hamburger (81) was able to isolate in the chick the brachial cord from ascending and descending tracts which have no effect on the proliferative activity of the cord or upon the differentiation of indifferent cells into motor neurons.

Barron (83, 84) examined a series of silver impregnated chick embryos to determine the normal motor neuroblast development. The brachial lateral motor column is established by neuroblasts recruited from medullary epithelium and also through differentiation *in situ* of indifferent mantle cells. Growing dendrites of neuroblasts have the capacity to induce indifferent cells to differentiate into neuroblasts. When the wing bud is amputated there is a reduction of the primary unipolar neuroblasts which usually become bipolar; fewer indifferent mantle cells develop into neuroblasts resulting in motor hypoplasia.

Limb ablation experiments on forty-eight to sixty-hour chick embryos, Bueker (85), were carried to three months after hatching. They produced cellular hypoplasia, 27 per cent in posterior column,

50 per cent in spinal ganglia, 90 per cent in the lateral motor columns.

By removing neural crest from the thoracic and lumbar regions of chick embryos in the fifteen to twenty-three somite stages, Hammond & Yntema (86) showed that the sympathetic ganglion cells of the paravertebral chain and the prevertebral plexuses arise from neural crest; the medullary cells of the suprarenal and abdominal chromaffin cells also. The preganglionic column is formed and its fibers establish the trunk sympathetic in normal pattern. There is no evidence that neuroblastic cells migrate from the neural tube to contribute to the peripheral sympathetic system [cf. (2)].

When mouse sarcoma No. 37 and No. 180 and Rous fowl sarcoma were substituted for the limb in chick embryos they developed tumors at the limb site (87). The lumbosacral nerves are well developed; the cells of the lateral motor column, however, are reduced 30 to 60 per cent but the spinal ganglion cells are normal or hyperplastic.

Hypophysis.—Transplantations into the sinus venosus have been used by Hegre (88) to test the developmental relationship between the nervous and epithelial components of the hypophysis. Pars intermedia may develop in transplants made at stage 35 or later and depends on the presence of diencephalic floor material (89).

Regeneration.—All the work reported here in regeneration is on amphibians. A complete review with a wide view of the literature can be found in Rose (90). Forsyth (91) amputated the hind limb in *Rana sylvatica* larvae through the middle or distal third of the thigh. Gradual reduction of regenerative capacity occurs at the onset of metamorphosis and completely disappears shortly after the knee joint is formed. Hypophysectomy alone or combined with thyroidectomy prevent regeneration of the hind leg of *T. viridescens* during a ten week period [Richardson (92)]. Administration of thyroxine did not assist regeneration; antuitrin-G, however, gave good growth response in hypophysectomized animals. With both thyroxin and antuitrin-G in animals with both glands removed, cartilage grew and bone differentiated.

Karczmar (93) investigated the specific effects of amputation and denervation on the regression of forelimbs of *A. punctatum* larvae. When nerve resection was performed four days after am-

putation, regression was accelerated. If the limb was denervated for ten days prior to amputation regression was slow.

In a series of papers, Singer (94 to 97) has given a most complete picture of the role of the nervous system in regeneration in adult *Triturus* together with the quantitative estimation of the number of nerve fibers necessary to initiate and complete the regenerative process. The quality of the fibers is not important, but the quantity is. The sensory contribution of a single nerve is adequate to cause regeneration, not because it is sensory but because it contains the requisite number of fibers. The threshold values for the arm components have been calculated in terms of surface area to be innervated. This series of papers has presented a keen analysis of a most involved problem.

Sperry (98) has investigated the eye muscle nerves in tadpoles and salamander larvae to find out whether normal motor coordination or incoordinate mass action would result after normal nerve muscle connections were produced. The oculomotor was roughly divided and allowed to regenerate. The author concludes that myotopic specificity of motor neurons is irreversibly determined at an earlier developmental stage in the oculomotor system than in the nerves of the limb.

Regeneration and degeneration experiments on the lateral line nerves and sense organs in anurans have been reported by Wright (99). After tail tip amputations the sense organs normally regenerate from placodal material from the most posterior organ or from one of the most posterior cluster. The regenerating lateral line accompanies the sense organ material. The lateral line nerve is not a necessary nor an inductive agent for regeneration and budding and organ regeneration, though it has trophic nerve action.

Unilateral excision of the mesencephalon in closed neural fold stage (100) results in restitution by an active proliferation of cells in the dorsal portion of the intact wall which migrate to fill in the defective side. When unilateral excision of the brachial region is performed there is complete restitution accomplished by cellular proliferation and migration from the contralateral half [Detwiler (101)].

After removal of the lateral half of presumptive hind brain in early neurula of *Amblystoma* the remaining neural fold bends across the midline, fuses with the ectoderm and closes the remainder

of the hind brain from the exterior [Harrison (102)]. Neural crest derived unilaterally distributes itself bilaterally. After the crest migrates the medulla is left as a half tube which soon closes either directly by apposition of dorsal and ventral margins, or by thin epithelial laminae extending from the margin.

Reproductive System

In a long term study, Phelps (103) has observed the reactions of intraocular endometrial transplants under varying conditions in monkeys. The vascular phenomena incident to nidation could be followed in every phase and with certain combinations of estrogen and progesterone the changes in the coiled arteries which are seen in the normal ovulating cycle could be reproduced. The postovulatory phase of the endometrial cycle involves a specific action of progesterone causing characteristic changes in the coiled arteries. Moore & Failor (104) have studied the role of sex hormones in the origin and development of uterine glands in the opossum. Ovarian influence on gland formation is manifest at ninety to one hundred days of development.

Hamilton (105) found that during estrus there are two well differentiated areas in the rat cervix, an upper, noncornified and a lower cornified region.When rats are raised from seventeen days postnatal on a vitamin A-free diet, Truscott (106) finds that ovarian wet and dry weights decline steadily but without correlation with body weight. Ovarian density rose with decreasing ovarian weight. The estrous cycle of the golden hamster can be followed by external examination or by the smear method [Ward (107)]. This form is exceedingly useful for the attack on developmental and physiological problems. Farris (108), by injecting urine of monkeys collected near the ovulation period into immature rats, produced hyperemia of the ovaries which lasted for five days.

Runner (109) has used the anterior eye chamber for the culture of fertilized ova, cleavage stages, morulae and blastocysts of the mouse. Implants remain visible for about three weeks, non trophoblastic structures seldom persist more than ten days.

By anastomosing the uteri of unilaterally ovariectomized rats, Krehbiel (110) has studied distribution of ova. Proximal unions were in general more successful in guaranteeing distribution of ova in the sterile uterus. Green & Winters (111) have secured and described segmentation stages of swine ova.

The time relations of cleavages and subsequent preimplantation stages of the hamster are described by Venable (112). Ovulation occurs during the middle of the night preceded by a receptive period of several hours. The ovum completes two cell divisions in the tube and enters the uterus at that stage during the latter half of the third day. Implantation occurs on the fifth day. Venable (113) has also investigated the volume changes in the hamster egg.

Colchicine has a decidedly toxic effect upon mouse ova [Waldo & Wimsatt (114)]. Intraperitoneal injections of 0.10 cc. of colchicine caused fragmentation of the tubal eggs. Concentrations of 1:32,000 produced inhibition lasting nine hours without lethal damage while 1:4,000 probably destroyed the ova. The eggs are more responsive than dividing cells of body tissues. Van Dyke & Ritchey (115) injected 0.06 mg. colchicine per one hundred gm. body weight. All the embryos died in animals injected during the early stages.

When rat metanephros, whether intact or macerated [Swartz (116)], is placed on the chorioallantois of the chick the undifferentiated kidney tissues grew but older tissues became necrotic. No species specific reactions were obtained toward either macerated or intact heterotransplants.

The mesonephros of the albino rat has been studied in the anterior eye chamber (117). Pretubular stages seldom give rise to tubules. The Wolffian duct does not induce tubule formation as it does in amphibian and chick. Once nephrogenesis has begun mesonephros will grow and differentiate in the eye. The tubules persist as grafts long after they would ordinarily regress.

Alden (118) has studied the osmiophilic lipids of the rat uterus during oestrous, early pregnancy, immaturity and after castration. The fat is unaltered in the interimplantation zones but is changed at the implantation site where it may be used by trophoblastic elements.

In a study of implantation phenomena Blandau (119) inserted glass or paraffin beads of approximately the same size as the blastocyst into the uterus of rats and guinea pigs between the second and sixth day of behavioral estrus. There was a definite difference in the two animals; in rats the foreign bodies implanted regularly causing a decidual reaction, while in the guinea pig the beads did not penetrate the epithelium and decidual reactions were minimal.

The primary trophoblast cells of the rat are identifiable as enlarged polar trophoblast elements with hyperchromatic nuclei, [Alden (120)]. On the fifth day, these cells increase in size and make contact with the uterine epithelium at the base and sides of the egg chamber. Rapid hypertrophy and hyperplasia of trophoblast elements follow. These giant cells are embryonic in origin.

Van der Horst (121) shows that in *Elephantulus* in contrast to other placentalia the trophoblast forms after the appearance of the segmentation cavity when differentiation of ectoderm and endoderm is already under way. Amnion formation occurs either by cavitation or by a folding over. The author considers cavitation as the more original form of amnion formation.

Reynolds (122) has studied the geometry and hydrostatic relations of the rabbit uterus during pregnancy. He divides the accommodation of the products of conception into three phases: preimplantation, uterine hypertrophy and uterine stretching.

Placenta

The histochemistry of the placenta and its correlation with the forming embryo is one of the promising fields of investigation. Wislocki & Dempsey (123) have found that the trophoblast shows pronounced cytoplasmic basophilia attributable to ribonucleoprotein; this disappears after mid-gestation and alkaline phosphatase appears and increases steadily to term. The trophoblast has been shown to be the region for producing placental steroidal substances. Glycogen is absent in the cat's placenta, as is iron. Phospholipids and ribonucleoprotein are present in the endothelial cells lining the maternal vessels. The uterine epithelium contains glycogen, lipoid droplets, basophilic substances, argyrophilic material and acid and alkaline phosphatases. The same authors have investigated the pig placenta (124) and the rodent placenta in a similar way (125).

Hard (126) has presented his study of phosphatase in the placental and fetal membranes of the guinea pig. Phosphatase is present in embryonic endoderm, yolk sac endoderm, plasmoditrophoblast (labyrinthine zone), junctional zone and decidua. Structures negative in phosphatase are subplacenta, cytotrophoblast, fetal mesenchyme and vascular elements of both placenta and yolk sac, ectoplacental trophoblast and trophoblast of the spongy zone, [Dempsey & Wislocki (127)].

In the sheep placenta the relation of the maternal and fetal vessels has been reported by Barcroft & Barron (128). The vessels are so arranged that the fetal blood leaving the capillaries is adjacent to the maternal blood entering them. This has been considered as a more efficient mechanism for exchange. While the fetal vascular bed is expanding the oxygen content of the umbilical vein increases steadily to a maximum and remains fairly constant 86 to 90 per cent saturation until one hundred days. It then tends to decrease until term in spite of an apparent increase in the maternal vascular net.

In studying the efficiency of the reversed flow in fetal and maternal vessels, Noer (129) has constructed artificial placentas by which hydrogen ions (hydrochloric-acid), methylene blue and glucose were tested with parallel and opposite directions of flow. Crossing the artificial placental barrier occurred in all cases with opposite flow—in none with flow in the same direction.

Noer & Mossman (130) have made a surgical approach to the problem of the function of the yolk sac placenta in the rat. In the last six days of fetal life the allantoic placenta with its circulation are requisite for fetal maintenance. The formation or functions of the yolk sac are still to be determined.

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PHYSIOLOGY OF REPRODUCTION[1]

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The current year has witnessed an increase in the number of publications bearing on the physiology of reproduction. The greatest emphasis has been concerned with mechanisms associated with pregnancy. Stress has been laid on histochemical phenomena and the distribution of enzyme systems in reproductive tissues. The significance of this work has yet to be elucidated by further study. New approaches have been made with regard to vascular structures in the uterus and ovary, the segmental innervation of the human uterus, and an adrenergic mechanism in the anterior hypophysis, at least in the rabbit. Significant advances also have been made with respect to relaxin, to our knowledge of hyaluronidase in semen, and to the metabolism of spermatozoa. Many publications contain details elaborating concepts and relations established in earlier years. Some of these suggest important avenues of experimentation which remain to be explored.

Sex Cycles

In primates.—A summary of the problem of adolescent sterility is made in a small book by Ashley-Montagu (1), the best chapters of which have been published separately (2). Van Casbricum (3) reported in an extensive study based on 6,212 natives of the Witwatersrand that the age at the menarche was 14.65 ± 0.04 years. This contrasts with 13.2 years cited by Mazer & Israel (4) for American girls in the second edition of their book on *Menstrual Disorders* which is a distinct improvement over the former one.

A study of the time of ovulation by Sevitt (5) revealed the presence of a secretory epithelium early in the cycle in two of ten patients. One had a well-developed corpus luteum on the 14th day of the cycle, and the other, a ruptured Graafian follicle on the seventh day. "Early" ovulation in the rhesus monkey was established by van Wagenen (6) in the Yale Colony by an incidence of 4.3 per cent pregnancies when twenty-two females were mated on

[1] This review covers the period from May 1, 1946 to March 31, 1947.

the sixth day of the menstrual cycle. Farris (7, 8), employing his test of ovarian hyperemia in the rat, detected ovulation in seven monkeys in the mid-cycle, but four of the monkeys gave no evidence of ovulation at this time. He has applied this test with reported success in many of a series of one hundred women. Ovulation in the puerperium has been studied by Lyon & Stanom (9), who, employing endometrial biopsies in lactating women, found that anovulatory menstrual cycles regularly occur during the puerperium. Meyer (10) restated his views concerning the anovulatory cycle, the primacy of the ovum, and menstruation, without resolving the issue to more than a difference in definitions between his view and the more conventional views that menstruation is independent of ovulation. Palmer (11) has given the most comprehensive recent review of the clinical value and physiological bases of the various tests for ovulation in women. The effect of contraceptive practices masking sterility from any cause is considered by Rubin (12).

An outstanding contribution to the anatomy and physiology of the gibbon is reported by Matthews (13), who notes that the uterus is flattened dorso-ventrally, like that of the chimpanzee, orangutan, and human, and unlike the gorilla and monkeys. The menstrual cycle of the gibbon, characterized by a scanty flow, was found to be 27.83 ± 4.07 days.

A careful study of hematocrit, plasma protein, and weight changes during the menstrual cycle in women is reported by Danforth *et al.* (14). Only when the data were grouped and evaluated statistically, could it be shown that hematocrit and plasma protein levels diminished before menstruation, while the weight increased. The trends were reversed with the onset of menstruation. Hauck (15) failed to find in more than thirty menstrual periods any regular variation in plasma or urinary ascorbic acid levels. The literature cited in this article on the subject is conflicting. Similarly, a careful study by Maw (16) failed to confirm earlier observations by Smith (17) on a shift in the creatine-creatinine excretion ratio during the menstrual cycle.

The response of the sex skin of the chimpanzee is reported in two papers. Clark (18) used estrogens and Clark & Birch (19) employed combinations of estrogen and progesterone. The former said that the sex skin of the prepubertal male of the chimpanzee is less responsive than is that of the baboon, while the latter found

that a much greater response could be obtained when both hormones were used in an optimal ratio.

In infra-primates.—Characteristics of the sex cycles of lower forms have been studied in a variety of ways. The way Brobeck *et al.* (20) measured the energy exchange in rats during the estrous cycle and pseudopregnancy is reminiscent of the running activity studies of a number of years ago. Similarly, a report by Morgan (21) contains important descriptive data on the sex cycle of the opossum which is reminiscent of the classical descriptions of the estrous cycle in the guinea pig and rat many years ago. A novel note is set forth by Engle (22) in a paper entitled, "No Seasonal Breeding Cycle in Dogs."

The relation of temperature and the thyroid gland to reproductive activity in rams was found by Bogart & Mayer (23) to be definite: as environmental temperature increased, reproductive activity diminished, but it could be restored by thyroid hormone. The effect on semen of elevated body temperature was similar to the effect of administering thiouracil. The view is held, therefore, that the thyroid determines the "relative" activity of the reproductive organs. Basal body temperature changes have been observed in rats, guinea pigs, and rabbits by Nieburgs *et al.* (24) in an attempt to elucidate the nature of the basal body temperature curve employed by gynecologists. Estrus was preceded, accompanied by, or followed by a decrease in body temperature. During spontaneous or induced pseudopregnancy, body temperature became elevated. In hens, body temperatures taken at two-hour intervals were shown by Fraps (25) to bear a fairly constant relation to ovulation and oviposition even when the time of laying was reversed experimentally.

The effect of progesterone on estrogen-induced estrus in anestrous sheep was observed by Fraps *et al.* (26). Progesterone, either by injection or from induced corpora lutea, promptly terminated estrus. At no time was there a suggestion of an estrogen-progesterone synergy in the induction of heat. On the contrary, injection of estrogen into pseudopregnant rabbits or into pregnant rabbits during the height of luteal function induced estrus in experiments by Klein & Mayer (27, 28). This period of estrus was associated with copulation, ovulation, and production of new corpora lutea.

The effects of introducing various unusual conditions on re-

productive capacities of rats have been reported in three papers. Auditory stimulation had no effect on breeding and rearing of albino rats as reported in 1944 by Farris (29); Cameron & Collings (30) observed that carbon monoxide, in one-half a lethal dose twice daily had no effect on reproductive capacity, or on the size or condition of the young; Nordskog (31), however, observed reproductive failure (fetal resorption) and agalactia in ergotized female rats.

A word of doubt about the anesthetic action of certain steroid hormones is expressed by Farson *et al.* (32) who state that it is a question of toxicity rather than anesthesia.

The Ovary

A number of publications concerning the structure and function of the ovary have appeared within the period under review. A review by Hisaw (33) summarizes modern concepts of the development of the Graafian follicle, and the mechanism of ovulation.

Ovulation.—An experimental study of ovulation by Dushkind (34) in the frog, hen, and rabbit was designed to test three hypotheses concerning ovulation: (*a*) smooth muscle fibers were demonstrated in the follicle wall of all three species; (*b*) proteolytic enzymes effected opening of the follicle only in the frog; and (*c*) cilia of the fimbriae were not necessary to act upon the follicle and attract liquor folliculi through a minute opening in the surface of the follicle. No positive evidence concerning the ovulatory mechanism is added in this study.

Fraps (35) established that in the hen, the first follicle of a clutch to discharge its egg has a lower threshold for gonadotropic stimulation than other follicles of the clutch. The time of release of ovulating hormone from the hypophysis in the hen precedes ovulation by five to six hours, according to Rothchild (36). A newly discovered spiral arrangement of the artery in the hilus of the rabbit ovary has been shown by Reynolds (37). This arrangement is believed to be the morphological basis for lowering blood pressure to near-osmotic levels and equalizing blood flow throughout the ovary. A detailed study of the development of fibrous connective tissue in the rabbit ovary has been made by Duke (38). Reticular fibers first appear about one week before birth, the fibres of the mesovarium giving rise to the epithelial core in the

medulla of the organ. Elastic tissues do not develop in the veins and arteries until about twenty days after birth. Abnormal structures have been noted in the human ovary: Erskine & Rannie (39) describe a case of bilateral ovarian aplasia, without other congenital anomaly, and Bacsich (40) has noted multinuclear ova and multiovular follicles in the human ovary.

Corpus luteum.—The structure of the corpus luteum has been the subject of four studies. Harrison (41) observed that the luteal cells in the mare are derived from the granulosa, reaching maximum development in ten to fourteen days. Mechanical rupture of the follicles leads to hypertrophy of the granulosa cells without luteinization. A similar effect in the rabbit was described by Friedman in 1932. In the cat, Dawson (42) describes the changes in the corpus luteum during lactation, with and without suckling. Everett (43) noted that histochemically detectable cholesterol (Schultz-Reaction) in corpora lutea of rats depends upon luteotropic stimulation. The possible role of cholesterol as a progesterone precursor is discussed by him in the light of experiments with estrogen and luteinizing hormone injections. Succinic dehydrogenase was found by Meyer *et al.* (44) to be highest when the corpus luteum is largest. The relation of this observation to the function of the corpus luteum is not known.

Gonadotropins and the ovary.—A number of reports on the effect of gonadotropins upon the ovary have appeared. Among these were one by Nalbandov & Card (45) on the effect of follicle stimulating hormone and luteinizing hormone on immature chick gonads; studies by Saunders (46) and by Bishop (47) on the effect of ovulation during diestrus in the mouse, and a report by Brown & Bradbury (48) on the production of pseudopregnancy in women by the injection of five to ten thousand international units daily of chorionic gonadotropic hormones.

An interesting new observation, recorded by Gaarenstroom (49), shows that when estradiol is given to hypophysectomized rats along with chorionic gonadotropin, ovulation and luteinization take place. The gonadotropin alone was ineffective in this regard except immediately after hypophysectomy. Prolactin was necessary for progesterone production (50) however. This work is reviewed in the Harvey Lecture by Laqueur (51). The determination of urinary gonadotropins in a test for ovulation in women and monkeys has been described in detail by Farris (52). Bunde (53)

found this test to be relatively unreliable, however, when used to detect early pregnancy.

Female Genital Tract

Tubes.—The lymphatic vessels of the human Fallopian tube have been studied by Ramsey (54). They are found to be abundant in the cavernous portions of the mucosal folds, and when moderately distended, they contribute largely to the main bulk of fimbriae. The embryonic development of the ligaments of the oviduct in the domestic fowl was studied by Kar (55) who found these structures to be under the hormonal control of the ovary.

Uterus.—The implantation of the rat ovum as related to osmiophilic epithelial lipids in the uterus is described by Alden (56) who finds an increasing concentration of these substances throughout the uterine epithelium in the first seven days of pregnancy. They disappear after castration, and are not found during pro-estrus. The relation of osmiophilic granules to preparation of the uterus for implantation or for the welfare of the ovum has not been shown. Krehbiel (57) studied the old problem of transmigration of ova in unilaterally ovariectomized rats in which he made eight types of anastomoses between the uterine horns. Transuterine migration failed when cervical openings remained separate or were joined just above the cervix, but it did take place when the uterine lumina were joined higher up in various ways. These observations confirm earlier ones interpreted to mean that the reversal of the direction of uterine contractions does not effect the distribution of ova in uteri. Uterine motility in such preparations has not been studied. In hens, Rothchild & Fraps (58) were able to influence the ovipositions of eggs by injection of pitressin, a result which is not surprising. The uterine glands of the opossum were shown by Moore & Failor (59) to grow rapidly under ovarian hormonal control between the ninetieth and one-hundredth days of life.

Other growth effects in the uterus were described by Koref & Engel (60) who showed the super-effectiveness of progesterone in the form of microcrystals when used locally, and by Forbes & Hooker (61) who employed the change of stromal nuclei from a fusiform to vesicular shape in a test for progesterone applied locally to a small segment of uterus in the manner described by

McGinty a number of years ago. The involution of the uterus of the cat was described by Dawson (62). He found that lactation did not affect the early involution of the uterus, but that it did accentuate later involution, the myometrium being progressively reduced as the endometrium is reconstituted. The special effect of steroid hormones on the distribution of alkaline phosphatase in the uterus of the mouse was described in a careful study by Atkinson & Elftman (63) who noted a differential distribution in the longitudinal and circular muscle layers respectively. It is not present in the stromal layer of the endometrium, but it is in other parts according to the prevailing hormonal status. McShan *et al.* (64) found the succinic dehydrogenase content of the uterus to be equal to one-fourth that of the liver, with evidence that the enzyme is concentrated in the secreting epithelium of the uterus. Here, again, the functional significance of these relations remains to be established.

The motility and activity characteristics of the uterus have been the subject of several important studies. Among these is the provocative little monograph entitled *Uterine Contractility*, by Murphy (65). This is a brief summary of the author's work limited to one technic applied to the last part of pregnancy in the human. A genuine advance appears to have been marked in a series of publications by Palmer & Liesse (66), and Liesse (67 to 70). The first adduces evidence that the *os internum* of the human uterus forms a functional sphincter, the tonus of which fluctuates with the menstrual cycle and is influenced by hormones. Tonus is lowest during menstruation (25 mm. Hg), highest in the secretory phase (55 mm. Hg) and intermediate (40 mm. Hg) in the proliferative phase. After injection of novocaine into the sacral ligaments, the tonus diminishes by 30 to 50 per cent (67), except during menstruation when there is no effect. Liesse concludes therefore that at this time physiological relaxation is complete. Other observations suggest that contraction of the isthmus sphincter is under parasympathetic influence and relaxation under sympathetic influence (68). This is confirmed by Rucker's (71) successful clinical use of epinephrine to relax contraction ring dystocia.

Opposed to the above are the observations of Gunn & Russell (72) on the response of the lower uterine segment of the human uterus *in vitro* to epinephrine. A notable paper by Danforth (73) describes the fibrous nature of the human cervix. He shows how

this provides a morphological basis for formation of the lower uterine segment during gestation.

By observing special technical precautions, for the first time (69) a characteristic pattern of e.m.f. potential waves are recorded from the cervix of woman. The waves are of 50 to 100 μv with 10 to 15 superimposed oscillations per wave. The longer waves have a duration of one second. They are regarded as the result of highly localized uterine contractions. In a few women, discharges of 500 μv were observed during menstruation and lasting for 10 to 15 seconds. These waves were not correlated with the occurrence of dysmenorrhea. An effort by Dill & Maiden (74) to record electrical potentials of the human uterus in labor were less fruitful.

The specificity of anaphylactic responses of the guinea pig uterus is questioned by the work of Winter (75) who showed that a uterus sensitized to both albumin and globulin is desensitized to both antigens when it has responded to either one.

The innervation of the uterus, and its disorders, have received a little attention this year. Freeman (76), confirming the old observations of Keiffer and others, identifies Vater-Pacinian corpuscles in periuterine connective tissue of the human uterus. These and ganglion cells were abundant up to the level of the internal *os*. Freeman gives an excellent summary of the literature of this complex subject. In discussing functional dysmenorrhea, Waters (77) re-evaluates the value of presacral sympathectomyl and Resnick (78) describes an unusual instance of unilateral dysmenorrhea associated with a uterine malformation. Repair of the malformation effected relief of dysmenorrhea.

The subject of functional uterine bleeding is a perennial one for gynecic physiologists. Novak (79) has reviewed the subject. from a clinical standpoint which is helpful for investigators, Markee (80) has restated his view of the relation of regression-vasoconstriction, local blood-flow and other factors in the endometrium which gave rise to menstruation. The essential correctness of these views for the rhesus monkey is definitely established, although studies on the human uterus by Schlegel (81) and Dalgaard (82) showing the presence in the human of arteriovenous anastomoses in increasing numbers in the endometrium during the menstrual cycle suggest that the menstrual mechanism may be modified in different types of uteri. Bartelmez (83) denies the existence of arteriovenous anastomoses in the rhesus monkey. It is

to be noted, however, that he did not employ the special injection technic used by Schlegel, and the latter did not work with the monkey. Irrespective of, or in addition, to the varieties of menstrual mechanisms suggested by the divergence of viewpoints expressed above, Smith & Smith (84) have expanded their views on the role of a locally produced euglobulin within the endometrium premenstrually as the "bleeding factor" which is dependent for its formation and release upon endometrial catabolism.

The endometrial vascular adjustments prior to nidation (late secretory phase) in the rhesus monkey have been described in great detail by Phelps (85) from extensive observations of intraocular transplants of endometrium. She emphasizes again that estrogens do not permit extensive growth of the endometrial coiled arterioles; that estrogen and progesterone do favor their extensive growth, with enlargement and anastomosis of the ends of two or more endometrial coiled arterioles at a time corresponding to nidation. This observation has been fully confirmed and amplified in an elaborate study of the vascular pattern of the endometrium of the pregnant rhesus monkey by Ramsey (86). These observations give point to the view expressed by Hasner (87) that we should think of the endometrial coiled arterioles not as a device to provide for menstruation, but rather as an adaptation for the special conditions of nidation. Liesse (88) has noted, in a kind of confirmation of the work of Phelps and of Ramsey, that endometrial spiral arterioles are not found in curettings of the human uterus in the proliferative phase, whereas they are found in about half the curettings in the early secretory phase, and are seen in nearly all curettings obtained in the late proliferative phase. The vascular architecture of the endometrium clearly is a determining factor in the pattern of menstruation, according to Phelps (89) who notes that the growth of the vascular tree during any given cycle is influenced by the amount and kind of growth which occurred in previous cycles. Many so-called anomalies of menstruation without a doubt have their basis in this observation. The use of ethinyl-estradiol and progesterone in anovulatory menstruation is described by Bickers (90) who re-established normal cycles in more than half his subjects by subjecting the uterus to fixed hormonal stimulation for several experimental cycles.

The successful use of prostigmine in a series of two hundred patients in inducing uterine bleeding in delayed menstruation in

the absence of pregnancy is described by Parrella (91). This accords with numerous previous reports, but a critical study of this procedure by Baldi (92) is less favorable to the use of prostigmine as a test for pregnancy.

Pregnancy

Somatic aspects.—The problems of physiology in pregnancy have been much stressed this year both from the standpoint of the obstetrician and experimentalist. Among the first are Hellman (93) who is interested in the effect of aging of the mother on the course of pregnancy, Rutherford (94) who is concerned with the preconceptional use of progesterone therapy in habitual abortion, and Tompkins (95) who adds to our knowledge of basal body temperature graphs in relation to the duration of pregnancy. Karnaky (96) has defied the tenets of those physiologists who produce fetal resorption in laboratory animals by giving estrogen in enormous quantities to pregnant women without ill effect. On the contrary, he used it with alleged success in threatened abortion. This confirms for women the high estrogen tolerance of pregnant monkeys reported last year by van Wagenen (97). Both of these observations are given meaning by the surprising report of Smith *et al.* (98, 99) that when estrogen is administered to pregnant women it gives rise to an appreciable increase the excretion of pregnanediol. Lyon (100) reports that pregnanediol excretion begins to diminish several days before the onset of labor, to a level of 10 to 20 mg. per day at term. The excretion of adrenal corticoids during pregnancy has been reported by Venning (101), who finds an increase during the first trimester of pregnancy at the end of which time they return to normal excretion levels. There is a secondary increase again in the very last part of pregnancy. Venning suggests that the excretion of corticoids is related to an alteration in carbohydrate metabolism. If so, this might be related in some way to morning sickness.

Zondek (102) has again focussed attention on the fact that after fetal death the hormone levels of the blood and urine remain high, but if fetal death is secondary to placental death the hormone levels in pregnancy diminish abruptly. This is affirmed by Hirsch (103).

Toxemia.—A search for the cause of toxemia of pregnancy in a placental toxin has been the object of several studies. It is alleged

positively by Schneider (104), but without benefit of real proof, that this substance is thromboplastin and its normal antagonist, antithromboplastin. A previous study by Schneider (105) showed in mice that the antithromboplastin levels increase appreciably in the last week of pregnancy. Another line of research, the physiological implications of which are not yet clear, shows that the blood of women in pregnancy inactivates posterior pituitary substances. Page (106) demonstrates a progressive increase until term. He finds (107) that the concentration of the enzyme in any week of pregnancy $= 6(\log_{10}[\text{plasma pitocinase}]+1.7) \pm$S.E. 0.7 weeks. Krieger & Kilvington (108) failed to find a correlation between an antidiuretic substance in pregnancy, nonpregnancy, the puerperium or toxemia in three hundred and three women. Woodbury *et al.* (109) find, as does Page, that in late pregnancy, human blood increasingly inactivates posterior pituitary substances. They conclude, accordingly, that a posterior pituitary substance is not associated with the onset of labor. A search by Bradshaw (110) for a pressor substance in human placental tissue yielded negative results.

Newcomer (111) has studied the interrelationships between the placenta, fetus, ovary and the development of anemia in the latter part of pregnancy in the rat. Some of her conclusions are open to question in several respects, notably, the statement that the ovary is necessary in the latter part of pregnancy to maintain living fetuses is not in accordance with Courrier's (112) direct experiment on the subject, and her conclusion that the anterior hypophysis offsets anemia in some undefined way neglects the older observations of Newton (113) and others to the effect that the placenta is the primary cause of water retention in the gestating organism. This view is supported by recent observations of Roscoe & Donaldson (114, 115). The relation of the reproductive state to the decline of induced hypertension in pregnancy has been studied this year by Page (116), Page *et al.* (117, 118) and by Sharkey & Hess (119). The results of these studies indicate that the decline in maternal hypertension is associated primarily with a maternal vascular change arising from placental function. Page *et al.* (116) add the fact that of the common steroid hormones only desoxycorticosterone offsets the decline in hypertension. It remains to be seen whether or not this is related to a physiological mechanism rather than a pharmacological effect. Page & Ogden (118) fail to

find experimental hypertension affected by estrous cycles, pseudopregnancy, or gonadotropic substances. Hill (120) claims that massive doses of stilbestrol do elicit a slight increase in systolic blood pressure in female rats and not in males. Sharkey & Hess (119) find that the fetal death rate is not higher in hypertensive women than in normal women.

Circulation rate.—The circulation time of blood-flow in normal pregnant women diminished according to Manchester & Loube (121) from arm-to-tongue, from arm-to-lung, and from lung-to-tongue as pregnancy progressed. The corresponding increase in circulation rate is not like that found in pregnant rabbits by Reynolds (122) who reported a diminished femoral-carotid body circulation time in the first half of pregnancy, an increase during the third quarter followed by a second decrease in maternal somatic circulation time in the last quarter of pregnancy. The rate flow of blood through the maternal uterus was found to diminish progressively until the twentieth day of pregnancy, whereupon there was a profound but transient ischemia of the uterus. With conversion of the conceptus at this time from a sphere to a cylinder, the circulation rate of maternal blood was restored to what it was in early pregnancy. This coincides with a period of rapid fetal growth. The hydrostatic basis of this, governed by the shape and size of the conceptus, is believed by Reynolds (123) to be attributable to the fact that the uterine tissue tension in the large sphere exceeds by many times that in the cylinder of equal radius, other conditions being equal. The role of this transient physiological ischemia is shown to be related to a high incidence of fetal death in late pregnancy (123). This is borne out in careful studies on fetal death in wild rabbits by Allen *et al.* (124). Fetal death in early pregnancy, Brambell & Mills (125) point out, is frequently associated with the occurrence of fibrin in the yolk sac contents of the embryos.

The placenta.—This organ has been the object of continued intensive study. Dempsey & Wislocki (126) have extended their detailed observations on the distribution of phosphatases in mammalian placentas. These have been found in placenta and in adjacent maternal tissues of the guinea pig, cat, sow, and woman. Phosphatases capable of splitting adenylic acid, fructose-diphosphate, glycerophosphate and lecithin are particularly abundant in syncytial trophoblast. In the cytotrophoblast, alkaline phosphatases only

are present, indicating that lecithin and glycerophosphate cannot be split there. Uterine glands of certain species are rich in acid phosphatases. Wislocki *et al.* (127) made similar studies of the placenta of the rodent. A quasi-quantitative study on the responses of placental tissues to stains of different pH is reported by Singer & Wislocki (128) by which curves of light absorption supposedly characterizing different proteins were obtained. Pratt *et al.* (129, 130, 131) have analyzed whole placental tissues by more conventional methods. The proximate composition of nine placentas was found to be: protein, 77 per cent of dry weight; fat, 3.8 per cent of dry weight; ash 8.6 per cent of dry weight. The water content was quite variable but averaged 87 per cent. Of the lipids, comprising 12.3 per cent of the dry weight, 3.51 per cent was neutral fat, 8.85 per cent, essential lipid. These were further analyzed into cerebrosides, free cholesterol, cholesterol esters and the various phospholipids. The vitamin contents were also determined, with measurements including biotin, niacin, pantothenic acid, riboflavine, and thiamine. Holzaepfel & Barnes (132) and Barnes (133) have noted the distribution of vitamin C in the human placenta. The details of all the above work make an impressive list of many essential constituents of the placenta, and even of the distribution of some of them within this important organ. It remains to be seen, however, what bearing all this information will have on our ultimate knowledge of the growth, function, and dysfunction of the placenta. Similarly, the electron microscope, as used by Mossman & Noer (134) in studying fetal membranes, holds promise.

The permeability of the placenta has been the subject of two reports. Wiener & Sonn (135) demonstrated that α and β antibodies (univalent) traverse the human placenta, whereas bivalent antibodies do so less readily. The practical conclusion, based on their observations, is that Rh glutinins are smaller bodies than Rh agglutinins. Wilde *et al.* (136) measured the permeability of the placenta of the guinea pig to inorganic phosphate. They found that, unlike water and sodium, inorganic phosphate reaches the fetus in amounts just about equal to the total phosphorus retained for growth. There is a wide margin of safety for water and sodium. Compared to sodium, phosphorus has a placental transfer coefficient which is two to three times greater than that of sodium. Perhaps the different conditions pertaining to phosphorus transfer rendered it difficult for Obermer (137) to deduce the optimal phos-

phorus intake during gestation in the human. Studying the relations of the fetal and placental blood vessels to each other in the sheep, Barron & Barcroft (138) noted an arrangement affording flow in opposite directions in parallel nets, comparable to the situation described in the human uterus by Grosser some years ago. The distance over which flow is opposite and parallel increases with advancing gestation—testimony to a nice mechanism assuring adequate placental transfer at the time when the fetus is growing most rapidly. This arrangement is found by Noer (139) to be the most efficient one for transfer of substances in "artificial placentas" made out of cellophane.

The rate of turnover of water in the human fetus is suggested by the observations of Vosburgh *et al.* (140) to the effect that a volume of amniotic fluid equal to one-third its total volume is replaced each hour. Sodium turnover is at the rate of once every 20.5 hours. These are lower rates of turnover than were found by the Carnegie workers in the guinea pig. Rivett (141) found that neither carmine nor insulin are absorbed from the human amniotic sac. Nevertheless excess amniotic fluid can be reduced by administration to the mother of ammonium chloride [Abrams & Abrams (142)].

Nutrition.—Studies of the effect of war-time nutritional conditions on pregnancy in the Netherlands and Great Britian are reported by Smith (143) and by Sutherland (144). In the former country, there were transitory effects of an adverse nature on gestation, and an increase in menstrual irregularities during a period of acute generalized undernutrition; in the latter, there were adverse effects on gestation due to conditions associated with unemployment, but not overcrowding. This is borne out in effect by the report of Burke (145) in the United States showing that preeclamptic conditions are more frequently encountered in individuals on a poor diet. With respect to specific nutritional factors, Wilson & Warkany (146) report induced anomalies of the genitourinary tract in vitamin A deficiency, and Popjak (147) notes that rabbits fed amorphous cholesterol during pregnancy acquire such heavy deposits of lipoids in the placenta that there is interference with fetal nutrition. Strouse & Drabkin (148) successfully treated hyperthyroidism during human pregnancy with thiouracil.

Vagina and Cervix

Hamilton (149) has made a quantitative study of the cellular

reactivity of the rat cervix to estrogen in different reproductive states. She notes that the cervix of the mature rat is more reactive than is that of the immature rat. Krehbiel (150) reports that pregnancy takes place after surgical removal of the cervix in the rat, and that at estrus in these animals the uterus is distended with fluid.

The detection of malignancy by cervical cytology is reported in a careful study by Ayre (151) who stresses that smears from the cervical *os* are better than vaginal smears for this purpose. Porphyrin, the active part of cytochrome-*c*, hemoglobin, peroxidase, etc., was found by Jones *et al.* (152) to be the product in cervical smears of bacterial organisms producing it. From experimental work on dogs, Sousa-Pereira (153) suggests that increasing the blood flow to the cervix by lumbar sympathectomy influences favorably the susceptibility of cancer of the cervix to radiological procedure. While his arteriographs do indicate that hyperemia results from this procedure, as might be expected, the physiological rationale of it is not clear. Langman & Burr (154) report the curious observation, which must be both confirmed and explained, that in fourteen cases of malignancy the cervix had a negative e.m.f. relative to the symphysis pubis, whereas in all but three normal subjects it was positive.

The use of the vagina as a test object for estrogens is reported by Hartman *et al.* (155) who find that local injection of estrogen into the vulva of the weanling guinea pig evokes opening in a time which is inversely proportional to the dose. The minimal effective dose is stated to be 2×10^{-7} mg. estrone. Lloyd *et al.* (156) employing rats in a similar manner, observed that 0.00025 mg. estrone is necessary, and that the paravaginal injection is much more effective than subcutaneous injection. Krichesky & Glass (157) demonstrated the presence of estrogen in intravaginal pellets of blood made from blood of normal, castrate, and climacteric women. The influence of distention and local irritation was not controlled by the use of inert pellets, however.

The cyclic variations in viscosity, pH, water-content and dextrose content of human cervical mucus have been studied by Pommerenke & Viergiver (158, 159, 160). These investigators find a marked pre-ovulatory increase in water content, dextrose content and acellularity. This just precedes a rise in basal body temperature, and is associated with "good" sperm penetrability. Estrogens

injected into castrated women gave rise to an increase in quantity and translucency of the mucus. Barton & Wiesner (161) studied sperm penetrability of cervical mucus, but they did not study this in relation to cyclic variations in the mucus.

Reproduction in the Male

Fertility.—The male factor in the problem of sterility is receiving increasing emphasis in discussions of clinicians, experimentalists, and veterinarians alike. A conference on *Problems of Sterilily* is summarized in the book edited by Engle (162), while a panel discussion led by Klussendorf & Hamilton (163) presents the problem as it relates to cattle. The effect of dilution of spermatozoa was found by Chang (164) to be a factor of primary importance in the fertility of rabbits since a small volume with a high concentration of spermatozoa is more effective than the same number in a larger volume of fluid. Thus both total count and concentration must be taken into consideration in evaluating semen samples. With regard to motility, Ivanov & Kassavina (165) found in the dog that prostatic secretion increases sperm motility under both aerobic and anaerobic conditions. This property is lost by prior heating of the prostatic secretion to 100°C.

Metabolism.—MacLeod (166), and MacLeod & Summerson (167), in a detailed study of sperm metabolism found that SH groups are necessary for sperm motility. Inhibitors, such as Ca^{++} and arsenicals destroy motility with attendant decrease in glycolysis. Tosic (168), however, stresses the fact that sperm motility depends upon an enzymic dehydrogenation and deamination in the presence of molecular O_2. One gains the impression that new facts remain to be discovered regarding this complex subject. In this connection, Mann (169, 170) has made extended observations on this subject also, finding that motility and fertility are proportional to the metabolism of glucose, confirming MacLeod's observation.

Hyaluronidase.—The role of hyaluronidase in fertilization has continued to receive attention. Swyer (171) has studied the hyaluronidase content of semen in the human and animals, finding a high statistical correlation between fertility and concentration of this substance. Kurzrok *et al.* (172) reviewed the subject, discussing the supposed series of reactions by which hyaluronidase may dissolve the granulosa cells about the ovum. They add data per-

taining to the clinical aspects of the subject. Leonard & Perlman (173) observed the greatest concentration of the enzyme in adult rat testes; there is little or none in immature rats, as is also the case after hypophysectomy. Thyroidectomy was without effect. Leonard *et al.* (174) employing a turbidimetric test (175) found that seminal vesicle fluid increases the concentration of hyaluronidase in rat ejaculate. Leonard & Kurzrok (176) extended their observations of this enzyme by studying inhibitors of hyaluronidase in granulosa cell dispersal. Blood serum of the rat, chicken, rabbit, horse, limulus, human, and cow inhibited bull hyaluronidase in dispersing follicle cells from rat ova *in vitro*. Only rat testis hyaluronidase was slightly inactivated by rat serum.

Reproductive tract and testes.—Sex hormones, obtained through the mothers' milk on male reproductive organs of rats was found by Price (177) to affect the gross size, compared to the controls, without alteration in histological appearance. The effect was apparent only at fourteen days, and not at the eighth, or twentieth day of the puerperium. Blair (178), injecting various sex hormones into juvenile *Bufo fowleri*, finds that this species reacts in a way comparable to mammals. Injection of pregnant mare's serum into immature male mice was found by Bishop & Leathem (179) to stimulate interstitial tissue and seminal vesicle weight, but it had no effect upon spermatogenesis. A careful study by Sluiter & van Oordt (180) of the cytology and function of testis interstitial tissue suggests that when this tissue is in a secretory condition the cells are devoid of lipoid granules. This may be regarded, accordingly, as an index of androgen output by interstitial tissue.

The Anterior Hypophysis

Interrelations between the anterior hypophysis and the sex hormones are discussed in the provocative article by Laqueur (51) to which reference has already been made. Papers dealing more strictly with this gland deal with its special cytology and function, however. Work by Hunt (181, 182) shows that estrogens injected into ovariectomized rats evoke a wave of mitosis in the hypophysis in forty-eight or more hours. Estrogen injected into pregnant rats has a similar effect, although the response is not uniformly effective. This observation may be related to the observation of Klein (27) in which estrus and mating were produced in pregnant rabbits

by injected estrogen, at a time when the hypophysis is considered generally to be suppressed. Wolfe (183) has noted that progesterone administered to immature rats restricts a post-castration increase in weight and prevents the expected increase in number of basophiles. A study by Bradbury (184) involving the use of both estrogens and progesterone in rats showed that the pituitary weight-increase evoked by estrogens alone could be prevented by progesterone. In addition to these effects, estrogen called forth a release of gonadotropic hormone as evidenced by increased ovarian weight, whereas progesterone did not call forth release of a gonadotropic substance. Curiously, if rats are castrated just prior to receiving estrogen, the gonadotropic titer of their hypophyses remains high. Smith (185) observed similar effects, insofar as the effect of estrogen on pituitary weight is concerned. Warwick (186) found the potency of the hypophysis of the ewe to vary with season, breed, and after spaying in accordance with evidence from other species.

An adrenergic link in the ovulating mechanism of the rabbit is quite clearly established by Sawyer & Hollinshead (187) who found that epinephrine in a dilution of 1:1000 caused ovulation in five of ten rabbits when injected into the hypophysis but not when given intravenously. Acetylcholine was without effect, as was electrical stimulation of the hypophysis and cervical vagi, according to Markee *et al.* (188). When the hypothalamus was stimulated, ovulation was observed to occur, however. Hertz & Meyer (189), performing hypophysectomy in proestrous rats, found that this operation prevented ovulation if done two hours after the start of proestrus, and before ovulation. From this they conclude that the hypophysis is necessary in order to secrete luteinizing hormone prior to ovulation. This is a plausible explanation which awaits direct proof but it agrees with a similar observation by Westman & Jacobsohn in the rabbit some years ago. Meyer *et al.* (190) found that the ovaries of immature rats remain sensitive to luteinizing hormone for many days after hypophysectomy.

With respect to lactation, Langezaal & Gaarenstroom (191) observed that prolactin neither initiated lactation in young rats nor maintained it in hypophysectomized rats, but that when this hormone was given in conjunction with cortin and glucose to hypophysectomized rats, lactation was maintained, just as it was when

whole pituitary implants are made. Francke (192) examined the effect of anterior pituitary tissues on ovarian tissue explants from immature rabbits and found no stimulation of ovarian growth, in contrast to what was found for testicular tissue under similar conditions. No explanation is given. Antihormone formation in response to gonadotropins results better from subcutaneous administration of the hormone than from intravenous administration, according to Leathem (193). Aging does not alter the ability to form antigonadotropins in rats.

Estrogens

In blood and urine.—The nature of the combined estrogens in the blood has been a topic of interest for a number of years. This year, several new contributions to our knowledge of this subject have been made. Roberts & Szego (194, 195) report that in human blood virtually all protein-bound estrogen occurs in the lipofraction III-O, which is β-globulin plus lipids. Under simulated physiological conditions, estrogen could be dialyzed out of human blood. There is some evidence that the site of formation of this estroprotein may be in the liver according to observations by Roberts & Szego (195). Boettiger (196) has worked at the problem from a different angle. He has studied the adsorption of estriol by plasma proteins *in vitro*, finding that estriol is strongly adsorbed by plasma protein in a manner that renders it only slightly filterable by the kidney. Of 6.43 mg. added to 100 cc. of plasma, only 0.40 mg. remained free. Jensen *et al.* (197) record the fact that the 60 per cent of the free estrone found in the urine of stallions is free estrone-sulfate.

The excretion of estrogens by the aglomerular kidney was a subject of study by Boettiger & Boettiger (198). In the toadfish, which has this type of kidney, these investigators found that both free and conjugated estrogens are eliminated chiefly in the combined form after injection of massive doses of estrogen. The elimination was very variable in three experiments, although results were definite.

Cholinesterase.—The relation of estrogens to serum cholinesterase was a subject of four reports, three by Sawyer & Everett (199, 200, 201) and one by Herschberg (202). The former find that ovariectomy of cyclic female rats results in a decrease of serum

cholinesterase to levels approaching that of adult males. Injection of estrogens restores it to levels which are normal for the female. Progesterone was without such an effect, whereas testosterone depresses the serum cholinesterase level to that found in the male. Sawyer & Everett followed the serum levels of some rats for a year and a half, from which they concluded that the cholinesterase level of the serum follows the estrogen-level of the blood. They conclude that estrogen stimulates the synthesis of this enzyme. In his elaborate, comprehensive study and review of the subject, Herschberg arrived independently at exactly the same conclusion. Testosterone proprionate was found by Kret (203) to elicit an increase in reticulocytes in the blood of adult rats. The effect was not attributable to the destruction of red blood cells, but rather to a decrease in the time necessary for maturation in the bone marrow. Perhaps somewhere in this general area of blood-enzyme-hormone relationships lies the answer to the sex difference in red blood cell count between the male and female.

Mention should be made in passing to the accomplishment of Furchgott *et al.* (204, 205) who have defined the infrared absorption spectra of estrogens, progesterone, and pregnane derivatives. While this is still in the realm of pure chemistry, it will add greatly to methods of hormone exploration of body fluids when further technical advances have been made.

Relaxin

Symphysis pubis.—Relaxation of the pubic symphysis in estrogen-primed guinea pigs is described Emery (206) to occur with desoxycorticosterone just as readily as with progesterone. Zarrow (207) found that the relaxation time for estrogen and progesterone given together is 10.5 days in ovariectomized, and 16.5 days in ovariectomized-hysterectomized guniea pigs. Thus while estrogen alone effects relaxation, progesterone accelerates the response provided the uterus is present. An interesting account of the histological characteristics of symphysis pubis relaxation is given by Talmage (208).

Relaxin.—The relation of the above effects to real relaxin is not known although it was stated definitely by Meyer (209) in a previous review that estrogen causes production of relaxin in the presence of the uterus. Albert *et al.* (210) point out that relaxin is a

substance containing 11 per cent nitrogen in water-soluble powder preparations having 20 to 30 units per milligram. An x-ray study of pubic ligament relaxation in the mouse by Hall & Newton (211) suggests that there is a difference in the characteristics of the relaxation process produced by estrogen and progesterone on one hand, and by relaxin on the other. Dewar *et al.* (212) point out that the vaginal response to estrone in mice is potentiated by relaxin in pregnant rabbit serum. The broader physiological import of these observations should be fully explored.

Sex Hormones and Cancer

Estrogens are the only normally occurring substances which give rise to cancer in pituitary glands, mammary glands, lymphoid tissue, and the uterine cervix under very special conditions. Such conditions have been reviewed by Gardner (213). Biesele & Gasic (214) report that sex hormones affect the size of chromosomes in transplanted I or Ia leukemia cancer cells in susceptible mice. Testosterone maintained them at the large size found in male hosts, whereas in females chromosomes became small, in the absence of androgens. Ovariectomy had no effect. The endogenous metabolism of sex hormones was accelerated in the presence of cysts and neoplastic lesions induced by 2-acetamino-fluorene, according to Cantarow & Paschkis (215).

In view of the well-known antitumoral effects of progesterone and testosterone described by Lipschütz and his co-workers, new observations on this are of interest. Iglesias & Lipschütz (216) noted that anhydrous hydroxy-progesterone *per os* prevents development of fibroids in guniea pigs but the effective dose is about fifteen times greater than when the steroid is given subcutaneously. Burrows & Hoch-Ligeti (217) could not detect any antitumoral effect of progesterone on mammary cancer in C^3H mice. This is in contrast to the report of Heiman (218) who found that progesterone in RIII mice brought about considerable reduction in the size of the tumors, and it prevented the accelerating action of estrogen upon them. Clinically, Hermann & Adair (219) failed to find a significant effect of testosterone on carcinoma of the female breast with soft tissue metastases. A dramatic reduction in size of uterine fibroids is described as occurring after administration of progesterone by Goodman (220) in each of seven women, but this

observation is in direct opposition to that of Segaloff *et al.* (221) who failed to find such an effect although they employed very rigorous criteria in order to evaluate the effect of their treatment. Apparently more critical judgment will have to be used in defining the age, stage, or type of fibroid which will respond to the antitumoral action of progesterone.

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CONDUCTION AND SYNAPTIC TRANSMISSION IN THE NERVOUS SYSTEM[1]

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In writing this section, the reviewer has been deeply indebted to the two excellent reviews by Bremer (11) and Grundfest (57) in the preceding volume. The whole field was then so exhaustively covered that it has seemed wise to restrict the present review to a critical survey of some fundamental problems. For example degeneration and regeneration of nerve were so fully treated that there was little to add this year, though reference should be made to the important paper by Erlanger & Schoepfle (38), of which a preliminary communication was reviewed last year. Special reference should be made to the comprehensive review on chemical transmission by Fuortes & Visintini (46). In the *Sensory Mechanisms of the Retina* Granit (54) has given an authoratative review of the neurophysiology of the retina. Unfortunately the long awaited monograph by Lorente de Nó had not arrived when this review went off to press. There have also been other regrettable deficiencies in the literature accessible to the reviewer, and no journals subsequent to May, 1947, were available. Some papers since published were seen in manuscript.

Permeability of the Plasma Membrane

There is still much confusion in regard to the properties of the plasma membranes of nerve and muscle fibres and it has not been relieved by two comprehensive reviews (61, 71), which, while assembling a wealth of data, have given little in the way of clear theoretical treatment. However, some problems are clarified in a more recent review by Wilbrandt (112). For the most part, neurophysiologists continue to think of a plasma membrane permeable under resting conditions to K^+ and H^+ ions and impermeable to anions and to larger cations such as Na^+ (52, 65). Precise permeability studies (10, 28) have falsified this view for muscle; and with both muscle and nerve the resting membrane

[1] This review covers the period from July, 1946 to May, 1947.

potential has also failed to show the predicted changes (the Nernst equation for diffusion potential) with variations in the external potassium concentration (10, 31).

It has been conclusively shown that the muscle plasma membrane is readily permeable to Cl^- as well as to K^+; for the criticisms of Krogh (71) have been answered by experiments in which the external concentration of potassium chloride was no more than 10 meq. per l. (28). It has now also been shown that with spider crab nerves the addition of potassium chloride to the external medium causes only a transient osmotic effect, much as with muscle; hence it is concluded (102) that the plasma membrane is freely permeable to both K^+ and Cl^- ions. Isolated nerve fibres of the frog show very low permeability even for water, which presumably is attributable to the myelin sheath, but it seems that K^+ and Cl^- ions do also penetrate (60). Shanes (102) and Conway (28) right warn against the customary procedure of compensating for added potassium chloride by abstracting an isosmolar amount of sodium chloride. When this is done, the nerve swells just as it would if urea were substituted for sodium chloride and irreversible changes occur in the membrane (60) rendering all such investigations suspect. This swelling has been attributed to a specific damaging action of potassium on the colloidal structure of the membrane (61, 62), a view which is disproved by the absence of swelling when, as above, potassium chloride is simply added without the sodium chloride abstraction, or when potassium is added with a nonpenetrating anion such as sulphate (29, 70).

However, when the external potassium falls below a certain concentration (about 10 meq. per l. for muscle), the plasma membrane ceases to have this simple semipermeability——permeable to K^+, Cl^- and other small ions such as HCO_3^-, H^+, OH^-, and impermeable to Na^+, Ca^{++}, Mg^{++} and the intracellular organic anions. Sodium penetration then occurs in the isolated muscle and nerve (28, 102, 104), though in the body resting muscles show sodium accumulation only when there is severe potassium deprivation (71). The process of soaking excised muscles (28) and nerves (105) in large volumes of fluid in some way increases the potassium concentration required to stop sodium entrance. It is of course possible that sodium accumulation may be prevented by active secretion of sodium outwards (the sodium pump), but

it has been calculated (28) that the resting metabolism of frog's muscle is quite inadequate to provide the energy necessary for the active extrusion of sodium if it penetrates the membrane as rapidly as potassium [cf. (71)]. Moreover, poisoning the metabolism by cyanide does not impair the exclusion of sodium (28).

Thus it has been shown that the permeability of the plasma membrane can be made dependent only on the size of the ion regardless of its charge (the Conway theory), but in the isolated preparation with low potassium concentrations in the external medium this exclusiveness is relaxed for sodium and probably other ions. This relaxation may be attributable to failure of the membrane to sustain a potential difference greater than about 60 mv. (10). It would appear to parallel the progressive decrease in membrane resistance of excised nerves (65).

Since under all conditions the plasma membrane is permeable to both anions and cations, a Donnan equilibrium will obtain across it, and the resting potential will be determined not by K^+ diffusion and anion impermeability, but by diffusion of both K^+ and Cl^- ions. The experimental testing of this inference (10) leaves no doubt that, with external potassium concentrations over 10 meq. per l., the membrane potentials are in accord with the Donnan equilibrium and the Conway theory, and not with the Bernstein theory of exclusive potassium permeability. Similar findings have been reported for spider crab nerves (102). As would be expected, the increased permeability of the membrane with low external potassium is paralleled by a potential lower than that calculated in terms of a Donnan equilibrium, but under such conditions predictions from the Bernstein theory diverge still further from the observed potentials. Notwithstanding these imperfectly understoood deviations, the Conway theory gives otherwise such excellent quantitative predictions in regard to diffusion and potential that it must be regarded methodologically as a sound basis on which to build in the further understanding of the plasma membrane. The subsidiary hypotheses developed (10, 102) in order to explain the deviations with low potassium, need further careful testing.

Conway (27) has refrained from extending his theory to nerve on account of the analyses of giant fibre axoplasm (5, 109), which give a product for the concentrations of potassium and chloride much greater than the surrounding medium (sea water). How-

ever, the axoplasm of such nerves had accumulated sodium during hours of soaking in sea water (105), and so a high potassium-chloride product would be expected, just as occurs with muscle under such conditions (10). In view of Shanes' (102) observations with spider crab nerves, the application of the Conway theory to squid nerves requires careful reinvestigation.

Cell Metabolism and the Plasma Membrane

The effects of anoxia and various poisons of enzyme systems on the resting potential and on impulse propagation of nerve (and nerve cell) establish that the membrane depends on metabolism for maintenance of its specific properties (3, 4, 56, 59, 60, 83, 90, 95, 113, 114). Continuing earlier work of Schmitt, several attempts have been made to establish a more precise relationship between metabolism and membrane function. Anoxia and poisons of the dehydrogenase-cytochrome-cytochrome oxidase system cause progressive depolarization, and blockage of impulses ensues when depolarization reaches a critical degree (3, 114). The effects are rapidly and completely reversible. By contrast narcotics block conduction by causing a rise of threshold with but little depolarization (6, 114). Kugelberg (80, 81) has continued his study of the changes in nerve excitability during and following ischaemia. When the excitability is accentuated by mild hyperventilation or by clinical tetany, first sensory and then motor fibres discharge spontaneously during the early phase of ischaemia, and also for a few minutes at the end of a period of ischaemia. Correspondingly the threshold of the nerve to direct stimulation is lowered during these periods, and accommodation is virtually absent. With continued ischaemia this hyperexcitable phase passes over to depression and eventually blockage [cf. (95)]. The postischaemic excitability also terminates in a prolonged depression.

Granit and his collaborators (7, 39, 55) have systematically studied the repetitive impulse discharges set up in a wide variety of mammalian nerves by cooling or warming. Large nerve fibres, particularly the afferent, are selectively excited by cooling, while warming excites the nonmedullated and δ-afferent fibres. This latter effect is of importance in investigating the reflex effects of impulses in small afferent fibres independently of the large fibre activity that is always a complication with electrical stimulation. Preliminary investigation shows that flexor, crossed extension and

nociceptive visceral reflexes are readily elicited by warming nerves, i.e. by small afferent fibres, and rarely by cooling. Cooling on the other hand elicits a powerful myotatic reflex by its stimulating action on the large proprioceptive afferent fibres in muscle nerves. It appears that temperature changes excite nerve by depolarizing the surface membrane through a depression of metabolism by the cold in large fibres, and by thermal inactivation of enzymes in small fibres (11). It is suggested (39, 55) that the greater sensitivity of afferent fibres is due to their slower accommodation, which again presumably is referable to a different metabolism. Finally temperature stimulation of nerve provides the only likely clue to the understanding of the operation of temperature receptors (7).

The fundamental work of Lorente de Nó on membrane potentials of nerve is foreshadowed in an analysis of barium action on nerve (90). The phenomena of after-potentials, prolonged electrotonic potentials and spontaneous discharges have been rigorously investigated and interpreted in terms of three basic components of the membrane potential of which only the quick and labile fractions have so far been described (90). The reviewer feels diffidence in discussing this important theoretical development until the comprehensive monograph is available, but it is evident that the complex reactions of nerves treated with barium or oxalate are effectively accounted for by these new concepts (90). It is also evident that such observations as those on ischaemia by Kugelberg (80, 81) are likewise explicable by membrane depolarization, which causes hyperexcitability when of moderate degree and depression and block when more intense (90). The prolonged post-ischaemic depression would be attributable to the accumulation of acid metabolites, e.g. lactic acid.

However, as we have seen above, the resting potential is dependent upon the movements of ions, and hence is directly related to membrane permeability. Metabolic disturbances [cf. (83)] probably affect potential secondarily by alterations they produce in membrane permeability. It is not yet clear how far the attempts to fractionate the resting potential (90, 101, 103) involve concepts of a mosaic-like fractionation of the surface membrane [cf. (51)], or alternatively concepts of several metabolic processes acting independently on the permeability of a uniform membrane. Moreover active secretions of ions must occur. For example there must be such a process for removal of the sodium leaking in during the passage of an im-

pulse or even slowly during rest, for the Conway theory of a purely Donnan equilibrium must be regarded as a first approximation (28). Such active secretory movements of ions provide an additional way in which changes in metabolism produce changes in resting potentials with the consequent fractionation of this potential.

Acetylcholine Metabolism and the Nerve Impulse

In 1947 Grundfest (57) gave a comprehensive and critical review of the experimental data relating to the interesting hypothesis that acetylcholine metabolism is intimately linked with impulse propagation, it being even causally related to the "breakdown" of the membrane that characterizes the active phase of the impulse (92). Since then there has been but little new supporting evidence. Grundfest himself adopts a fairly conservative attitude towards Nachmansohn's hypothesis and points out that the experimental evidence shows no more than that "the acetylcholine system enters into the activity of excitable conductile tissues at a more crucial stage than do, for example, oxygen and other metabolic systems." Though superficially it seems that Nachmansohn and his co-workers have presented very convincing arguments for this latter statement of the hypothesis, the following criticisms tell heavily against it [see Gerard (47) for other criticisms].

(*a*) The yield of acetylcholine on extraction of sensory nerves, dorsal roots, and postganglionic orthosympathetic nerves is no more than 1 per cent of that for ventral roots (42). Correspondingly the choline acetylase activity of dorsal roots and optic nerve is also only about 1 per cent of nerves known to have cholinergic terminals (43). Nachmansohn & Berman (93) give rather higher values for optic nerve choline acetylase (2 to 3 per cent of ventral root). Even such values are so low that it appears most improbable that acetylcholine metabolism is concerned with impulse propagation in sensory and postganglionic orthosympathetic nerves.

(*b*) Much importance is attached to the action of cholinesterase inactivators in blocking the transmission of nerve and muscle impulses, but it now seems likely that such blockage is not due to the inactivation of cholinesterase. It is to be noted that in their comprehensive investigations Nachmansohn and his co-workers (18, 19, 20, 21, 58) have always used concentrations of the anticholinesterases, physostigmine and DFP, high enough to block transmis-

sion and then have demonstrated an associated cholinesterase inactivation and a partial recovery [usually to about 20 per cent but recently (58) only to about 7 to 10 per cent of cholinesterase activity] when transmission was restored. It is therefore of great significance that, when nerve is soaked for hours in a much lower concentration of DFP (3m*M*), there is no disturbance of nerve impulse transmission, and yet there is virtually complete inactivation of cholinesterase (9) [cf. also (97)]. Attention should be drawn to the very high concentrations of anticholinesterases that are required to block nerve transmission. For example 0.0025 mM. DFP completely inactivates cholinesterase *in vitro* (92) and yet nerve has to be soaked in solutions at least one thousand and even ten thousand times stronger in order to produce block. Such a discrepancy may be attributable to the postulated situation of the cholinesterase on the inside of the plasma membrane, but the results of Gerard and co-workers (9) show that the inactivation of cholinesterase occurs with much lower concentrations of the anticholinesterases than are required for blockage [cf. also (97)].

(*c*) Originally the failure of action of acetylcholine and prostigmine on nerve impulse transmission was attributed to their inability to penetrate myelin and this was demonstrated for prostigmine (21). However with the extension of the hypothesis to muscle and to nonmedullated nerve (19) the barrier action presumably is relegated to the plasma membrane. It is possible (but not yet demonstrated) that the plasma membrane also normally prevents prostigmine and acetylcholine penetration while allowing physostigmine and DFP penetration; but this cannot hold for the activated plasma membrane, for impulses certainly cause the liberation of acetylcholine from cholinergic nerve terminals. Hence acetylcholine should be able to penetrate muscle and nonmyelinated nerve fibres when repetitively stimulated. Lorente de Nó (89) found that, with medullated nerve soaking in 0.9 per cent acetylcholine, even fifty thousand impulses caused no failure of nerve impulse propagation. Similarly no effect was observed during repetitive stimulation of the nonmedullated fibres of the grey matter of the frog's spinal cord (35) while soaking in 10^{-3} acetylcholine plus adequate anticholinesterase. Thus it would appear that the propagation of impulses is not disturbed by application of high concentrations of acetylcholine to the interior as well as the exterior of nerve fibres.

If then, as it appears, acetylcholine metabolism is not intimately related to the function of impulse propagation, what is its function in nerve fibres? As Loewi (88) points out, there is a close relationship between both the acetylcholine content and the choline acetylase activity of nerves and the function of their terminals. When these act cholinergically, the whole nerve fibre has a high acetylcholine metabolism, when adrenergically a high epinephrine (or nor-adrenaline) metabolism (41). The significance of this is best appreciated in regeneration. The cholinergic terminals are cut off and yet the regenerating fibre by reestablishing functional connection shows that the branches inherit the acetylcholine metabolism of the parent fibre. Conversely in cross-union experiments functional connection is not restored with sensory nerves regenerating to muscle (110) for then presumably the regenerating fibres are unable to develop an acetylcholine metabolism which is virtually absent in the parent fibres. However, an interesting exception has been reported by de Castro (24) where regenerating sensory vagal fibres were able to establish functional synaptic contacts [apparently noncholinergic and probably electrical, cf. (32)] with the ganglion cells of the superior cervical ganglion.

The Membrane Theory of the Nerve Impulse

Hodgkin & Huxley (64) have recently provided the first precise estimation of the potassium leakage during the nerve impulse. After first showing that the electrical conductivity of isolated crab axons is trebled by increasing potassium chloride in the external medium from 10 to 30 m.eq. per l., and that a similar increase in sodium chloride has no measurable effect, they found that the conductivity of the axon is also increased several fold after a brief tetanus, and slowly returns to normal over several minutes. Since this restoration is immediately effected by a brief immersion in sea water, there is no reason to doubt "that activity is associated with the leakage of a substance the effect of which on the nerve membrane is very like potassium." Calculation based on this assumption shows that about 1.7×10^{-12} moles of potassium leak through 1 sq. cm. of the membrane in one impulse, which would be more than sufficient (about twice) to discharge the membrane capacity in the manner required by the membrane theory of the nerve impulse. If the recovery of the conductivity to normal indicates a process of potassium absorption across the membrane, it occurs at

a rate of about 3×10^{-10} moles per sq. cm. per sec., which can be satisfactorily explained by the Conway theory. However it is important to realize that on that theory the escape of potassium during activity must be associated either with a transient membrane permeability to sodium (so that ingoing Na^+ ions exchange with outgoing K^+ ions) or with a diminution of the intracellular indiffusable organic anions. The former alternative has been demonstrated by Euler *et al.* (40) who observed an increased uptake of Na^{24} during stimulation of the sciatic nerves of cats. However their observed uptake of Na^{24} by resting sciatics may have been entirely into extraaxonal tissues and provides no evidence for sodium permeability of the resting plasma membrane. Since presumably ionic movements across the plasma membrane are causally related to the resting and action potentials, this work raises important theoretical questions: for example, how far is the action potential attributable to a transient period of exchange between external Na^+ ions and internal K^+ ions? Also, it is perhaps worthy of note that, on the membrane theory of the nerve impulse, outwardly flowing current will circulate from the region of the wake into the active region and this also should carry potassium out into the surrounding fluid. Hence, as was actually observed (64), the loss of potassium should be higher than for the mere discharge of the membrane capacity.

The electrical properties of giant crustacean axons have been exhaustively studied by Hodgkin & Rushton (65), who in addition give a precise mathematical treatment of the flow of weak rectangular currents through a nerve fibre both in the extrapolar and intrapolar regions. The basic assumptions are those of classical nerve theory, the leaky capacitative membrane separating a cylindrical conducting core from the external conducting medium. Theoretical deductions and experimental observations are in close accord and give confidence in the values derived for membrane resistance and capacity and axoplasm resistance; and for various derived constants such as the space and time constants. There is a fairly large scatter in these values, especially in those for transverse membrane resistance, which falls progressively in successive determinations on the same fibre. Presumably this is due to deterioration of the fibre and parallels the abnormally increased permeability already evidenced by the sodium uptake of isolated nerve and muscle. The membrane resistance of the crustacean nerve fibres is

several times higher (average over 2000 Ω cm.^{2}) than the values for squid fibres, but the capacity (average 1.3 μ F cm.$^{-2}$) is approximately the same. Parallel permeability studies should be of great interest.

Incidentally Hodgkin & Rushton find evidence for a rectifier action of the surface membrane, but they regard their experiments as being equivocal in regard to inductance. The usual absence of oscillatory behaviour at the cathode during a constant subthreshold current is related to the much higher transverse membrane resistance of the crustacean axons—averaging about ten times more than the squid axons (65). Correspondingly, in crustacean axons oscillatory potentials are observed at the cathode after the initial spike discharges set up by a continued suprathreshold current, which would greatly lower membrane resistance. No trace was observed of the "anodal local responses" observed by Arvanitaki (2) in sepia giant axons, nor were these observed even in squid fibres by Cole & Curtis (26). It appears to the reviewer that these anodal responses are merely the first wave of oscillatory membrane responses(1) attributable to the inductance-capacity-resistance circuit of Cole (25), and that the transverse membrane resistance of the sepia giant axons is so low that even the increased resistance at the anode is not sufficient to prevent damped oscillatory responses. However the initial wave at the cathode is much larger than at the anode, and it appears to be composed of a local response superimposed on the first oscillatory wave [cf. (2), Figs. 1 and 4]. Thus responses of nerve involving an increase in membrane polarization are envisaged as being passive oscillatory phenomena explicable in terms of its resting electrical properties (and hence electrotonic in nature), while the responses of depolarization are composed partly of such passive oscillations and partly of active responses—the local response of Hodgkin (63). Such a difference would account for the difference in critical thermal increments of the initial anodal and cathodal waves (2, 23). Sepia, squid and crab nerves would form a series with decreasing tendency for oscillatory responses, probably on account of the increasing transverse membrane resistance.

It is of great significance that Katz (67) has at last been able to establish the existence of local responses in frog's medullated nerve. By ingenious balancing technique he has so reduced the shock artefact and the electrotonic potential that the local responses dominate the potential picture set up by just subthreshold

stimuli. In their time course and in their relationship to stimulus intensity these local responses agree remarkably well both with the responses evidenced by excitability changes some ten years earlier (66) and with the local responses recorded from crustacean giant fibres (63). Thus for these diverse tissues as well as for mucsle (72) it has now been shown that a propagated impulse is set up only when a critical area of the surface membrane is activated. This is virtually a corollary of the membrane theory of the nerve impulse (99). Katz offers a theoretical explanation of local responses and their growth to fully propagated impulses, which is based on an assumed relationship of membrane resistance to membrane potential, but which is in good accord with experiment. He is able in this way to derive curves for membrane potential following brief shocks, which show a striking resemblance to actual records of local responses. Nevertheless the explanation fails to account for the observation (65, 69) that, during the passage of a just subthreshold rectangular current, the potential recorded at the cathode is much greater than at the anode; indeed it demands the reverse. To the reviewer it seems necessary to assume that the membrane battery is diminished, abolished or even reversed during the so-called active responses, whether local or propagated. Transmembrane stimulation of impaled muscle fibres shows that, in accordance with membrane theory, stimulation is produced only by outwardly penetrating currents, and that the voltage-capacity curves resemble those with surface stimulation (52).

Neuromuscular Transmission

The transmitter and the endplate potential.—When the cholinesterase of the curarized frog's sartorius is inactivated by prostigmine, physostigmine, or DFP, the endplate potential set up by single or repetitive nerve volleys shows a double phase of decay, an initial quick phase with a half time of about 20 msec. and a slow phase with a half time of one to three seconds (37, 45). When the cholinesterase is normally active, the fast decaying component is relatively much larger than the slowly decaying, which may be barely detectable. Apart from the striking difference in time course, these two components have reacted similarly to every test. Both are similarly diminished by soaking the muscle in stronger curarine or in acetylcholine (45), and both rates of decay have a temperature coefficient of 1.1 to 1.5, which is approximately the value for a diffu-

sion process (37). At the onset of repetitive stimulation there is a brief phase of potentiation during which the successive endplate potentials are increased above the initial value (44), and then follows a decline to a subnormal size. The slowly decaying component added by each successive endplate potential shows an exactly comparable potentiation and decline (37). It may be accepted that the slow component is due to acetylcholine; hence this precise correspondence indicates that the fast component is also due to acetylcholine. The double phase of decay may be explained by an extension of the hypothesis of the spreading surface action of acetylcholine (36). If the endplate membrane by its high sensitivity to acetylcholine (73, 74) is sharply separable from the surrounding membrane [cf. the histological distinction by Couteaux (30)], then outward diffusion of the liberated acetylcholine from the highly sensitive endplate focus to the surrounding membrane and from thence outwards into the tissues generally would explain the double decay curve and also all the other observations. The brief initial phase of potentiation during repetitive stimulation would be attributed to mobilization of the preformed acetylcholine of the nerve ending so that it is readily diffusible, and the subsequent decline to subnormality indicates the exhaustion of this store [cf. (107)].

Following injection of Ringer containing high potassium, Walker & Laporte (108) report a prolonged diminution of endplate potential and a depression instead of a potentiation of a second response. It seems likely that both effects are due to an exhaustion of the acetylcholine store in the nerve terminals, an effect relatable to the well-known effect of potassium in causing acetylcholine liberation (16).

The endplate potential and the muscle response.—All recent work on electrical responses of muscle (vertebrate and crustacean) fits in well with a generalization which has been most concisely stated by Katz & Kuffler (68).

> Probably, in all types of muscle tissue, an endplate potential or a catelectrotonic potential can exert two separate actions (provided it is large enough): it can set up (i) a propagated disturbance of the muscle membrane, and (ii) a local activation of the contractile substance.

This catelectrotonic potential can be set up either electrically or pharmacologically (75), and, if no propagated impulse arises, the contractile response is called a contracture. Kuffler (75) has also

shown that diminution of such a pharmacologically produced catelectrotonic potential by direct application of an anode decreases or abolishes the contracture.

Thus the causal relationship is between membrane depolarization (not action current flow) and contractile mechanism. This is most convincingly shown by a comparison of electrical (cathodal) and pharmacological contractures. The direction of current flow through both the membrane and the subjacent contractile mechanism of the muscle is diametrically opposite in these two conditions; and both types of contracture are abolished by application of an anode, which acts inversely on these currents, for it would increase the current flow generated by local pharmacological action. On the other hand in all such experiments there is a complete correlation between depolarization of the plasma membrane and excitation of the contractile mechanism. The only exception appears to be the β inhibitory action on crustacean neuromuscular transmission (78) whereby inhibition of muscle contracture is produced in the absence of any demonstrable effect on the resting potential or endplate potentials of the muscle. This strange anomaly merits further investigation—histological, electrical, and mechanical—for it appears that the inhibition has been exerted on an intracellular mechanism. In conclusion it would seem that a mechanism of transmission must be postulated whereby a depolarized plasma membrane on the surface of a muscle fibre activates the contractile mechanism throughout the whole cross-section of the fibre.

The relationship of endplate potential to contractile mechanism is well illustrated by the small motor fibre system to frog's skeletal muscle (76, 77, 79, 106). Microdissection studies show that the small nerve fibres are widely distributed to frog's skeletal muscles, probably innervating the same muscle fibres as the large motor fibres. Impulses in the small fibres set up local potentials (76, 77) exactly comparable with the endplate potential of curarized muscle or of crustacean muscle (68). With repetitive stimulation these local potentials summate, and an appreciable muscle shortening occurs at frequencies of 2 to 3 a second and quite large contractions (up to 15 per cent of the maximal twitch) at high frequencies. As with endplate potentials, the local potentials rapidly decrement away from the nerve endings, and correspondingly the contractions are localized to these regions, being sharply distinguishable from the propagated responses set up by large fibres.

Preliminary work indicates that these small fibres are reflexly very active and hence may be of importance in postural tone (79). However it is doubtful if the small motor fibres effect any appreciable contractile action in mammalian muscles, for even on repetitive stimulation they evoked little or no tension in the cat's gastrocnemius (84).

Synaptic Transmission in Ganglia

In an effectively illustrated paper Larrabee & Bronk (82) describe an investigation into prolonged changes (up to five minutes) in the synaptic excitability of the cat's stellate ganglion that ensue after its repetitive stimulation either presynaptically or antidromically (i.e. by postganglionic stimulation). (*i*) Following antidromic stimulation there is merely a prolonged depression (up to three minutes). (*ii*) On the other hand, presynaptic stimulation is followed by a phase of increased synaptic excitability, which builds up to a maximum and then slowly declines over several minutes. (*iii*) However, such facilitation is not observed when synaptic excitability is tested by a preganglionic volley in different fibres from those repetitively stimulated, there being then a depression much as is observed after the antidromic stimulation. Such evidence justifies their conclusion that the facilitation is due to some poststimulatory enhancement in the synaptic stimulation exerted by preganglionic fibres.

Other features of their observations have, however, been neglected in their discussion. Thus the initial phase of increasing facilitation (*ii* above) corresponds closely to the phase of depression observed with *i* and *iii*. Since in *ii* there would be the same ganglion cell excitation as is produced in *i* and *iii*, the associated depression would also be expected, and hence we may attribute the phase of increasing facilitation in *ii* to this passing off of ganglion cell depression. For example the prolonged rise of facilitation in their Fig. 6C after 1440 preganglionic volleys corresponds to the prolonged depression in Fig. 9 after 1200 antidromic volleys. Now excitation of ganglion cells either synaptically or antidromically is followed by a positive after-potential which is greatly lengthened by repetitive stimulation (32), and which consequently would provide an explanation of the phase of depression [cf. (12)]. Similarly the positive after-potential of the repetitively stimulated presynaptic fibres might provide an explanation of the prolonged

facilitation; for, as Bronk (12) has suggested, there would be an associated increase in the spike potential with a corresponding increase in its synaptic excitatory action. The alternative suggestion that the facilitation is due to an environmental change produced around the ganglion cells by some transmitting agent (acetylcholine or potassium) would seem to be effectively excluded (82). However, in the presence of an anticholinesterase, the accumulation of acetylcholine would undoubtedly cause a prolonged facilitation, for it produces a depolarization and after-discharge of the ganglion cells persisting for many seconds (32).

Invertebrate giant fibre systems offer unique opportunities for investigation of synaptic transmission. In general such synapses in the squid (17), cockroach (98), and crayfish (111) possess the same characteristic properties as vertebrate synapses—irreversibility, synaptic delay, facilitation, and inability to transmit such high frequencies as the constituent nerve fibres. The local potentials at such synaptic junctions are of great interest, but only with squid (17) was an attempt made to record them. When transmission was blocked by repetitive stimulation, a negative potential wave still appeared in the postsynaptic element. It is clearly a synaptic potential and is regarded as homologous with a local response, for it is similarly related to spike discharge (63). In every respect these observations of Bullock conform with the predictions of the electrical theory of synaptic transmission (34).

DFP was found by Roeder *et al.* (97, 98) to cause alternating periods of discharge and paralysis of cockroach ganglia, hence it has been concluded that acetylcholine is the synaptic transmitter. However prostigmine and physostigmine differ from DFP in that they block without showing intermittent excitatory action, as also does acetylcholine when applied with DFP, but not with physostigmine, as an anticholinesterase. These and other findings are difficult to reconcile with a transmitter action of acetylcholine, and it seems probable that it is not justifiable to assume that the effects produced by DFP are relatable to its anticholinesterase action.

Synaptic Transmission in the Spinal Cord

Excitation.—By taking special precautions with the monosynaptic myotatic reflex, motoneurones have been subjected to synaptic excitation by a single volley uncomplicated by interneuronal activity, which has been eliminated by employing very small afferent

volleys (85), by anaesthesia (14, 33) or by both. Three methods of stimulation (synaptic, direct, and antidromic) are available for testing the time course of subliminal excitatory events thus set up in motoneurones. The synaptic testing stimulation is applied by a volley in another monosynaptic path—the classical method of the facilitation curve. Lloyd [(85), Fig. 3] has now given this curve its final standard form, the maximum at zero test interval decaying exponentially with a half time of 2.8 msec. Unfortunately this method necessarily gives only the time course of decay of the excitatory process. The other two methods test the motoneurone's excitability by more briefly acting stimuli (either a direct electrical stimulus or an antidromic volley), and hence give facilitation curves showing after a synaptic delay (0.4 msec.) an abrupt rise for about 1 msec., and, after a rounded summit, a decay with approximately the same half time as the synaptic facilitation curve (14).

A focal needle electrode and an indifferent electrode have been used by Brooks & Eccles (14) to record the potential changes at the actual synaptic region during a synchronous synaptic bombardment. By various tests the complex potential has been shown to be composed of an initial diphasic spike due to the presynaptic volley, and a local negative potential of the motoneurones [the β potential of Renshaw (96)] with a rise to a rounded summit in about 1 to 1.5 msec. and a decay with a half time of about 1.5 to 2 msec. This is the same synaptic potential that was recorded after electrotonic spread to the ventral root (33), and has exactly the same synaptic delay (about 0.4 msec.). This delay is measured between the observed time of arrival of the presynaptic volley in the motor nucleus and the initiation of the synaptic potential. It is shown that the time course of the actual synaptic potential set up in the motoneurones will lie between that recorded with focal electrodes and the much slower potential recorded from the ventral roots; hence it would have a time course of decay very similar to that determined by the facilitation tests (14, 33, 85).

The focally recorded potential gives a relationship between the presynaptic spike potential and the synaptic potential, which is in close accord with the predictions of the electrical theory of synaptic transmission (34). It is further to be noted that according to this theory the presynaptic impulses set up local responses of the postsynaptic membrane immediately under the synaptic knobs,

and from thence catelectrotonus spreads to the remaining surface membrane of the motoneurone. Thus the synaptic potential will be in part due to local responses and in part merely to a passive catelectrotonus.

Lloyd (85) still argues for the existence of a detonator response in addition to the synaptic potential and its associated facilitation. However it would seem that whatever evidence there has been for the detonator response can be assimilated to the concept of the "local response" component of the synaptic potential. Thus it may be concluded that synaptic transmission can now be simply attributed to the foci of local responses set up in the postsynaptic membrane. When the involvement of an area by these local responses exceeds a critical intensity, an impulse will grow up and spread over the soma and thence down the axon, much as occurs with a local response of a nerve fibre growing up to a propagated impulse (63). If it is below this intensity, the local responses die out and the surrounding catelectrotonus decays exponentially as the membrane is recharged by its intrinsic battery.

Inhibition.—Two recent contributions, one experimental, the other theoretical, have provided a much needed clarification in the problem of central inhibition and have closely related it to the electrical theory of synaptic transmission (34). Experimentally Llyod (85) has shown that the so-called direct inhibition is exerted by the large afferent fibres of a muscle on the motoneurones of antagonistic muscles. Such an afferent (I) volley is pitted against the monosynaptic excitatory (E) volley in the afferent fibres of the antagonist. By observing at various IE intervals the inhibition of the reflex response evoked by E, an inhibitory curve is constructed, which in its simplest form rises from zero at zero IE interval to a maximum at about 0.5 msec. interval and thereafter decays exponentially with about the same half time as the unitary facilitation curve (85). Essentially the new inhibitory theory of Brooks & Eccles (13) attributes inhibition to the anelectrotonic action [cf. (2, 11, 100)] exerted on a neurone by the synaptic knobs of Golgi II cells that are generating a synaptic potential. The short axon with its terminal knobs provides the "source" for the currents flowing in through the "sink" on the soma. Thus the "direct" inhibitory fibres would act on motoneurones by means of the synaptic potentials they set up in Golgi cells which have synaptic knobs on those motoneurones. If such knobs are intermingled with knobs from the

monosynaptic excitatory fibres, the subjacent anelectrotonic areas would be strategically placed for limiting the growth and fusion of the local responses set up by the excitatory impulses (cf. excitatory theory) and hence would exert an inhibitory effect. Such an inhibition would have precisely the time course of the above IE curve. Furthermore the predicted limiting effect on the growth of the synaptic potential has been directly observed (15). If, on the other hand, the I volley sets up such a large synaptic potential in a Golgi cell that an impulse is discharged, then the initial inhibitory action exerted by its synaptic knobs would be expected, after about a millisecond, to give place to an excitatory action, which is precisely the effect observed by Lloyd (85, 86). Thus any Golgi cell is envisaged by the theory as potentially having both an inhibitory and excitatory function according as its synaptic potential is not or is adequate to evoke the discharge of an impulse. The implications of this dual role of Golgi cells are so far-reaching that the mechanism of every reaction of the central nervous system needs reconsideration (13). This is particularly so with the cerebral cortex where Golgi cells form such a large proportion of the neuronal population. It should be pointed out that the present excitatory and inhibitory theories may be regarded as a development in the light of modern neurophysiology of the original theoretical concepts of Sherrington—the central excitatory and inhibitory states—and readily explain all that was explicable by those concepts.

Lloyd (86, 87) has greatly clarified the problem of reciprocal innervation by showing the reciprocal pattern of action of afferent fibres from a limb muscle—excitation of that muscle and its synergists and inhibition of its antagonists. Such excitatory and inhibitory interactions link the muscles of a given joint into a myotatic unit, which has been diagrammatically related to the inhibitory theory (13). There is at least one interneuronal relay in the excitatory and inhibitory pathways to the muscles acting at adjacent joints (86), and with reflexes elicited from cutaneous and mixed nerves the reflex pathways are still more complex (8). Cutaneous afferent impulses from the forelimb also usually act on motoneurones of the hind limb by complex paths, but there is a direct inhibitory path to the flexor longus digitorum (91).

Two other theoretical explanations of inhibition have been suggested. Renshaw (96) finds that a dorsal root volley inhibits the monosynaptic reflex discharge with a latent period about 1.5 msec.

shorter than its inhibitory action on the soma spike set up by an antidromic volley in the same motoneurones. On the basis of this and other evidence relating to the β wave he suggests that "direct" inhibition is due to inhibitory impulses exerting a blocking action on the excitatory presynaptic fibres. However direct recording of the presynaptic volley shows that inhibition occurs in the absence of presynaptic blockage (15). Furthermore there is no diminution in the initial rate of rise of the synaptic potential even in deeply inhibited neurones, nor is there initially any detectable inhibition of the antidromic soma spike [confirming Renshaw (96)]. Hence the inhibition is exerted specifically on the reflex discharge of impulses. All these observations accord with the electrical theory of inhibition (13). Gesell *et al.* (50) have further elaborated the theory that the excitatory and inhibitory actions of synapses are due to their location, those on the soma being excitatory, those on the axon hillock inhibitory. Admittedly depolarization at one such site gives an opposite flow of intracellular current from the other; but the theory completely fails to explain inhibition, for *ex hypothesi* the reflex discharge of impulses is generated by depolarization of the axon hillock, an effect which is directly produced by the postulated action of the inhibitory impulses.

Acetylcholine and synaptic transmission.—Calma & Wright (22) report a potentiation of extensor reflexes by physostigmine, but, as this usually did not occur in the spinal animal, it may be attributed to some undetermined action on higher centres. Now that the synaptic potential has been established as the primary effect set up by the synaptic transmitter, it is just as important in investigating the nature of the synaptic transmitter as is the endplate potential for neuromuscular transmission. Experiments employing more indirect tests for synaptic transmission now have relatively little significance.

Inactivation of the cholinesterase in the frog's spinal cord (isolated in oxygenated Ringer and either with or without anaesthesia) has no effect on the synaptic potential set up by single or repetitive stimulation (33, 35). Furthermore the addition of acetylcholine in concentrations as high as 10^{-3} has only a moderate depressant action. This contrasts with the neuromuscular junction where a greater depressant action is exerted on the endplate potential by 1/500 times that concentration of acetylcholine (45), i.e. the mechanism in the spinal cord has less than 1/500 times the

sensitivity to acetylcholine. Hence in view of the extremely low acetylcholine content (42) and choline acetylase activity of dorsal roots (43), it may be concluded [cf. (88)] that acetylcholine plays no significant part as a transmitter in the monosynaptic pathway through the spinal cord. Thus the electrical theory of synaptic transmission (34) provides a satisfactory explanation for the spinal cord, which contrasts with the neuromuscular junction where transmission appears to be exclusively cholinergic (see above).

Neurophysiology of the Retina

The recent polarization experiments of Granit & Gernandt (48, 49, 53) on the retina emphasize still further the close parallelism that exists between retinal and spinal cord responses. There is firstly the whole syndrome of responses of the on-element: on-effect, PII potential (scleral surface of retina negative to vitreal), catelectrotonic potential in optic nerve, impulses in optic nerve. Responses of on-elements are potentiated by passage of current with cathode on sclera, and are depressed during the reverse current. Thus the on-element closely parallels an excitatory pathway through the spinal cord, and it gives precisely the responses that we should expect for transmission from sensory receptors to bipolar cells to ganglion cells and so to optic nerve fibres. The catelectrotonic potential in the optic nerve indicates that in part at least PII is the synaptic potential of ganglion cells. The PI potential may possibly also be matched in the spinal cord by delay path activity through interneurones. The off-elements set a more perplexing problem. Here we have undoubtedly a close association between inhibition of the optic nerve discharge and the PIII potential, which is recorded inversely to the PII potential (54), i.e. with PIII the "sources" are located on the scleral side of the "sinks." If PIII is a synaptic potential, it would have to be set up in neurones so orientated that they receive their synaptic excitation on the pole directed towards the vitreal surface of the retina. It is hard to see how this could occur for the horizontal cells, but Polyak (94) describes such neurones (the centrifugal bipolar) as being abundant in the retina, and other amacrine cells may also come into this category. Such neurones might well exert an inhibitory influence on the on-element pathway upstream from the ganglion cells, just as has been postulated for Golgi cells in the

spinal cord (13). Indeed an ingenious suggestion along these lines has already been advanced for the action of neurones of the off-elements (49). However the effects of polarizing currents necessitate a complicated explanation, because the off-elements are stimulated to give their characteristic off-effect by the same direction of current (cathode or sclera) that excites on-elements, and similarly for the reversed polarization. Hence one must postulate that the polarizing current acts on off-elements in that part of their path where they are orientated similarly to on-elements, and that, as shown by the PIII potential, they exert their inhibitory effect on the on-elements during the later reversed part of their path that occurs through centrifugal bipolars for example.

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SOMATIC FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM[1]

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Reduction of space allotted this review prevents reference to two-thirds of the articles abstracted,[2] rigidifies organization, and compresses style. Fortunately Lloyd's survey (1) in Howell's *Textbook of Physiology* clarifies existing theories of nervous conduction and intercellular transmission and codifies the principles of spinal reflexes, enabling a beginner to follow the recent work in the field.

Introduction.—In the reflex, action proposed by efferents diminishes peripheral change prehended by afferents. Hence the reflex is amenable to present mathematical treatment of negative feedback. Imposed on the simplest, or monosynaptic, myotatic arcs of the cord are hierarchies of more comprehensive arcs homeostatic for more complicated changes, the higher exciting and inhibiting the lower so as to reduce information at all levels. Thus conduct minimizes sensation.

To apply quantitative theories of communication to nervous activity requires the properites of single connections and details of statistical organization. Rashevsky, Householder & Landahl (2) have been most active with approximations by simple differential equations; Rosenblueth, Bigelow & Wiener (3, 4), Pitts & McCulloch (5 to 8) with analysis in terms of all-or-none impulses. Both need more histological information and input-output curves like Lloyd's.

First order arc.—Recent experiments (9) confirm Eccles' electrotonic theory of central synaptic transmission (10). In a neuron

[1] The period covered in this review extends from August, 1946 to August, 1947.

[2] For preparation of these, we are indebted to Barbara Wiener.

the cell plasm is an excellent conductor and is surrounded by a semipermeable polarized membrane of constant capacitance. The permeability decreases with flow of current into the cell, increases with flow oppositely directed (11). If an alternating current is sufficiently low in frequency to allow ion migration through the membrane, the effect of the impedance should vary as the degree of polarization or permeability (12). The permeability of a resting membrane is about eight times that of the same membrane with a current flowing in at 15 microamps. using an electrode 500 micra square (11). Accordingly, with antidromic volleys to provoke facilitation in motoneurons, or direct cathodal stimulation of nerves, or transmission in the nerve-block model of the synapse, the stimulating pulse is monophasic because the membrane is continuous, and little delay should occur in the response (12). The topological situation at the synapse is different. There, current channelled through the axoplasm of a presynaptic fibre flows out through the terminal membrane but into the recipient membrane, and this occurs with the initial positive phase of the action potential. The recipient membrane, its permeability decreased, ought to show the effects of impedance, and the voltage change should lag behind that of the terminal membrane (12). This in fact occurs, is called synaptic delay, lasts 0.3 to 0.45 msec. depending on the duration of the negative spike in the terminal membrane (10), and falls within the limits of the phase angle measured by Cole (averaging 76°) (13). Because of the inertia of ionized particles, the permeability of the membrane should lag behind the action potential, altering its descending phase at the focus, especially if the membrane also has, as Cole contends, an inductance (14). Eccles, however, is hesitant to accept this and ascribes the large and graduated responses of the recipient membrane to a "specialization" of the postsynaptic region (9, 10).

The negative synaptic potential, recorded in the recipient membrane locally, builds to peak voltage in 0.8 to 1.8 msec. and decays with a time constant of 1.6 to 3.0 msec. (9). Spread of current through the cell plasm being instantaneous, the "synaptic-potential" recorded from the ventral root reflects, with some distance-decrement, the moment-to-moment sum of electrotonic events in all the membrane of motoneurons proximal to the electrode. Its rising phase lasts 3 to 4 msec., and its time constant of decay is prolonged to 7 to 10 msec. (15). Residual facilitation, measured by

orthodromic volleys should have a time constant of decay between that of local patch and that of axonal sum. Lloyd had found it to be 0.45 msec (16).

Eccles thinks the dorsal root potential (d.r.p.) represents a catelectrotonus of afferent terminals in ventral horn and internuncial pools (17). He believes it is initiated by the local response of postsynaptic membrane and decays slowly with intrinsic recharging of the condensers in terminal membrane through its own resistance. Although accounting for some of the observed time relations, this fails to explain how, under deepening narcosis, the rising phase of antidromically initiated d.r.p. remains constant and the decaying phase of all d.r.p.'s, no matter how initiated, increases tenfold. But, suppose the arborized endings of dorsal root fibres are excited by catelectrotonus propagated along the postsynaptic neurosome, forming a great number of peripheral circuits with no impulses propagated beyond the smallest twigs (except for coincidence) because of increased area at each junction, as at "axon hillock," then these circuits must leak back randomly through the postsynaptic membrane, and better through a mosaic of decrementally propagated catelectrotonic patches than through wide sweeping bands of soma spikes or spike-like potentials. Narcosis will then favor steeper rising phase and prolonged decay in orthodromically induced d.r.p. but will not affect the rising phase in antidromically induced d.r.p. for the initiating catelectrotonus will have arisen symmetrically around the axon hillock of each motoneuron.

Lloyd describes residual inhibition having an incremental phase of 0.5 msec. and an exponential decay with time constant of 4 msec., mirroring facilitation (16). He considers it unreasonable to assume inhibition to occur anywhere except at the terminal region of the presynaptic fibres or at the somata of motoneurons. Brooks & Eccles have constructed an electrical hypothesis of central inhibition (18) as follows: Following subthreshold excitation, the soma of a Golgi II cell with short axon develops a catelectrotonus which causes a relatively large current to flow with small decrement through the synaptic knob (whose permeability is accordingly increased) into the immediately subjacent membrane forming there an anelectrotonic patch, which, because of the rectifying properties of the membrane, is at lower potential gradient but greater area and stabler in proportion than a self-channeling (19) catelectro-

tonic response. This effect supplementing that of the initial positivity of the diphasic presynaptic impulse would limit the degree of subsequent catelectrotonus and surround it with a barrier of raised threshold. The incremental 0.5 msec. is the time of one synaptic delay. With increase in afferent stimulation of the Golgi cell, it will be fired and facilitation should appear at the end of two synaptic delays plus intramedullary conduction time, even as Lloyd had shown, the postinhibitory facilitation occurring 1.5 msec. after a conditioning volley sufficient to excite internuncials (20, 16). This scheme accounts for inhibition in nervous nets whose fine structure is random and yields a greater diversity of actions in circuits with a given number of elements. It gives significance to the position of internuncial pools in the cord where premotor neurons end in a dorsal net, and it suggests that the termination of bulboreticular inhibitory fibres be sought in the ventrolateral portion of the zona intermedia or in the ventral periphery of the anterior horn, for both regions have short-branch neurons surrounding and playing upon the mass of motoneurons (21). [No similar hypothesis applies to fibres suppressing activity of crustacean muscle at the myoneural junction (22), for these are the slenderest of the motor group, having no sudden widenings or peculiar endings (23).]

Lloyd has noted that residual facilitation and inhibition in two-neuron reflexes are limited to motoneurons of muscles acting at the joint moved by the muscle whose afferents are stimulated. Thereupon he defines the myotatic unit as "the mutually dependent muscles of a joint together with the reflex paths that bind them" (24). Myotatic units are independent centrally but are bridged peripherally by two-joint muscles and mechanical interdependence of parts. Rosenblueth & Wiener's work on clonus should supply information about the natural period of this unit (25). Rhythmical variations in excursion and frequency of rhythmical movements waits explanation probably based on their work (26). Perkins (27) has concluded that the rhythmicity of shivering is determined by the resonant frequency of circuits involving proprioceptors and strongly resembling that of reflex clonus.

On the efferent side, Kuffler (28) has investigated in the frog a small-nerve motor system which is tonically active reflexly for posture and only evokes local potentials and local shortening around the myoneural junction. It is blocked peripherally by cura-

rine in concentrations which do not affect the twitch response set up by larger fibres. This complements nicely the earlier work of Bremer (29) who sought to explain by Wedensky inhibition the differential effects of small doses of curare on tonus and movements, and recognized clearly that the mechanism for posture was qualitatively different from that for movement. Further investigation of the same sort in mammalian muscle and cord may discover not only a peripheral separation of two sorts of motor functions but also clarify the existence of two brain-stem facilitatory systems.

After an antidromic volley, microelectrodes in the ventral horn recorded a set of repetitive potentials beginning at 1500 per sec. and occurring with decreasing frequency (30). Renshaw thinks these arise from single units and that such repetitive response may be the normal activity of some types of interneurons. In the published records the lower element is apparently firing at submultiples of the faster frequency, but axonal collaterals and reverberating circuits have not been excluded, and interpretation is difficult.

On the sensory side, work on causalgia proceeds slowly, peripheral anatomical pathology being still in doubt. "Cross-talk" from sympathetic and motor fibres to sensory fibres in injured peripheral nerve, notably the finer afferent components, has been shown electrically in beast (31a) and clinically in man (31b). Surgery has been largely directed to breaking this vicious circle before the conduct of the central nervous system is affected irreversibly. Induced pain of short duration has been shown to give lasting analgesic effects (32), and effort angina has been long relieved by temporary local block of somatic trigger areas (33).

Second order arc.—Quantitative studies on reflexes involving internuncials are scarce. Bernhard & Rexed (34) located an internuncial pool in the lateral part of the zona intermedia, feeding by one synaptic delay into motoneurons. Bernhard (35) discovered that moderately strong stimulation of the popliteal nerve produced successive reflex volleys in the peroneal nerve with initial central reflex time and period of 2.5 msec. Increase of stimulus strength shortened the rhythmic response tailwise until only the first volley remained, whereas a subliminal popliteal stimulus left a fluctuating level of facilitation of about the same period. He ascribes these effects to reverberating chains.

Maling & Acheson (36) remarked stepping movements with forward displacement of the body and righting reflexes in low decerebrate and spinal cats under *d*-amphetamine. Asymmetric body contact and muscle tensions systematically disturbed from those of normal antigravitational stance provide a massive organized stimulus that ought to institute organized intersegmental and crossed reflexes if the functional paresis following surgery on the nervous system is overcome. McIntyre & Lloyd (37) have reported that afferent volleys arising in the forelimb "inhibit some motoneurons of the ipsilateral lumbosacral cord with a latency sufficient for conduction and a single synaptic delay in the cervical cord, and facilitate lumbo-sacral neurons only after a further delay of several milliseconds." Low-threshold, group II, afferent fibres seemed responsible for the inhibition, and group II and III afferents for facilitation. The inhibition apparently occurred on the internuncial level since monosynaptic reflex discharges were little affected.

Sperry (38) has critically reviewed functional reorganization in central nervous tissue following injury and found that little return of function occurs except as a result of learning which itself has drastic limitations. Thus splicing different nerves together, or surgically changing the action of a muscle upon a joint, even if the motor nerves are the same segment or the muscles move the same joint, allows appropriate activity only if the perversion from the original function is slight. Transplanted extensors are not efficient flexors. Learning only serves to modify perverted action mostly by splinting for stability. Some more positive effects have been claimed, but they required continued conscious effort, never becoming "innate."

Third and fourth order arcs.—Following Magoun & Rhines' discovery of a bulbar mechanism inhibiting a wide variety of motor performance (39, 40) ranging from myotatic reflex to cortically induced movement, McCulloch, Graf & Magoun (41) described a path from area 4-s descending in the internal capsule where it gives off collaterals to the caudate, thence passing through the basis pedunculi, bending dorsally at the lower border of the pons where it decussates incompletely, to end in the bulboreticular inhibitory formation. Thence impulses pass down the ventrolateral portions of the cord. That myotatic reflexes are inhibited shows that some direct, or propriospinally relayed, connections are made

in the neighborhood of motoneurons. No impulses pass back to the cortex from the bulboreticular inhibitory formation, and the suppression of electrical activity of the cortex on stimulating 4-s is mediated by an arc through the caudate and thalamus (42).

Lateral to the inhibitory bulboreticular formation, stimulation gives facilitation of movement over the same wide range. Magoun (43) has shown this to be due to a descending facilitatory system beginning in the diencephalon and passing down, probably with relays, into the cord. Again, since monosynaptic reflexes are affected, connections probably go directly, or by spinospinal relay, to the motoneurons. Lloyd's (44) studies demonstrate that fibres do descend from medulla directly and by propriospinal relay to motoneurons where they may serve to set the stage for impulses arriving by the pyramidal tract which are delayed in the dorsal internuncial pool.

An additional suppressor pathway has been traced by Snider, Magoun & McCulloch (45) from the Purkinje cells of the cortex of anterior lobe and paramedian lobule to the fastigial nucleus, and thence to the bulbar inhibitory mechanism. The suppressor activity of the fastigial nucleus is not maintained in the absence of cerebellar cortex, nor is that of the bulboreticular formation in the absence of cerebellar and cerebral projections to it.

Similarly, Bach & Magoun (46) noted that the vestibular nuclei served as an excitatory mechanism for the cord. Unilateral destruction of the vestibular nuclei or interruption of the ventral funiculus of the cord abolished "decerebrate" extensor rigidity and reduced phasic reflexes on the injured side. In cats rendered spastic by ablation of the pericruciate cortex, removal of the vestibular nuclei only partially reduced extensor hypertonus and did not diminish hyperactive reflexes or clonus. Soriano & Fulton (47) found that extirpation of the anterior lobe in monkey failed to cause marked augmentation of positive supporting reactions with spasticity. These only developed in the extremities contralateral to the cortical lesions if area 4 and 6 were also removed. The tegmental and vestibular systems, both exerting excitatory influence on the cord, are independent, having distinct paths. The tegmental is chiefly concerned with movement and the vestibular with posture. Since both the lateral vestibular nucleus and the suppressor bulboreticular formation receive impulses from the fastigium, an interesting reciprocal system presents itself for study.

Immediate clinical importance of the bulboreticular centres can be demonstrated in the problems of spasticity and Parkinsonism. Wagley (48) has shown that interruption of the reticulospinal fibres produces spasticity without paralysis in macaques. Ranson, Bard, Richter, and Kennard [cf. (43)] had made lesions in the basal ganglia, hypothalamus, and subthalamus and noted mask-like facies and poverty of movement. Kelly, Beaton & Magoun (49) coagulated in the central midbrain destroying the periaqueductal grey and adjacent tegmentum beneath the superior colliculus and found that faciovocal activity was greatly reduced or abolished, confirming Bailey & Davis' (50) finding of akinetic mutism with lesions of the periaqueductal grey. These probably represent impairment of the brain-stem facilitatory system resulting in hypokinesia. Tremor at rest, but abolished by movement, has been produced in monkeys by destroying the ventromedial midbrain and pontile tegmentum without injury to the corpus striatum, subthalamus, or substantia nigra (51). In one case the lesion was in the facilitatory region, not encroaching on the suppressor bulboreticular formation. This alternating 8 to 10 per sec. tremor developed only several days after the operation although the monkeys were able to move about before then.

The cerebellum has finally yielded to localizors. Bard and coworkers (52) ridded dogs of motion sickness by removing pyramis, uvula, and nodulus of the cerebellum, although reflex vomiting persisted for spoiled food and apomorphine. Nims & Nulsen (53) found that each muscular contraction elicited from the cortex can be inhibited by stimulation in a topical area of the cerebellum with precise localization. Although this occurs in cats, similar stimulation in monkey gives facilitation (54). In cats and dogs, the centralis serves the hind-limbs, culmen and simplex the fore-limbs, midline areas flexion, and lateral areas extension. Hampson, Harrison & Woolsey (55) had reported that brief stimulation of the medial three-fifths of anterior lobe gave ipsilateral flexion (or extension inhibition) and contralateral extension where prolonged stimulation gave profound ipsilateral inhibition of extension with marked rebound of ipsilateral extension and strong contralateral extension continuing after cessation of stimulus. Brief stimulation of the lateral two-thirds gave active ipsilateral extension with rebound ipsilateral flexion where prolonged stimulation gave an initial active ipsilateral extension reversing to ipsilateral extensor

inhibition and followed by strong rebound ipsilateral flexion. They found localization of the neck in lobulus simplex and the tail in the lowest folia of centralis. There is overlap as indicated by simultaneous effects in trunk and fore- and hind-limb musculature from stimulation on either side of the fissure separating culmen and centralis. In another paper (56) they add that the strongest effects in cat's tail are obtained from lingula. In cat and dog, simplex in addition to controlling the neck and eyes gave opening and closing of the jaws and contraction and relaxation of orbicularis oculi, orbicularis oris, and nasolabialis. The paramedian lobule served with the upper folia, face; with the middle folia, arm; and with the lower folia, leg and tail. Flexion and extension were usually ipsilateral but sometimes bilateral. Inhibition was not prominent. Pyramis bilaterally affected arm and leg, and tuber vermis conjugate eye movements. In the monkey the lateral portion of anterior lobe, giving initial ipsilateral active extension, is more developed than the medial giving ipsilateral active flexion with extensor inhibition.

When these results are compared with Snider & Stowell's study of sensory representation in the cerebellum (57), it is seen that the map is much the same. The startling thing about this is failure to find any cerebellar potentials on proprioceptive stimulation.

Wilson & Magoun (58) ablated the inferior olive and report myoclonus in the ipsilateral vocal cord, intention tremor of the neck muscles, some head and body sway on standing, and decomposition of movement and hypermetria in the contralateral leg associated with extensor hypotonus and hyperactive patellar reflex. Bilateral lesions gave the same signs bilaterally. Tegmental and bulboreticular responses were unaffected. Grundfest (59), tracing its afferents, found that the impulses in or along the dorsal spinocerebellar tract provoked the earliest and largest activity in the inferior olive.

The superior colliculus was shown by Apter (60, 61) to have a point-to-point logarithmic mapping (with fovea zero) of the contralateral half of the visual field. In anesthetized cats illumination of an eccentric point in the field turned the eye to centre on the light when strychnine was applied to the homiotopic point on the colliculus. These findings, with Crosby's data (62, 63) on the microscopic anatomy of the colliculus permit the construction of a

powerful theory of tectal reflex action as part of the mechanism whereby we know universals (64).

There has been little new work, save anatomical, on diencephalon and basal ganglia. Sweet, McCulloch & Snider (65) found complex repetitive movements on stimulating the basal ganglia in cats and monkeys after transection of the cerebral peduncles. Caudate, pallidum, amygdala, and ventral or subthalamus gave such responses predominantly contralateral, beginning at the trunk and spreading distally. The hind-limb was activated by dorsal, forelimb by intermediate, and mouth and tongue by ventral portions. Acute decortication did not alter these responses. Frequency of response increased with voltage of stimulation until prevented by a tonic component. Voltages just insufficient to elicit movement sometimes diminished tone and frequently reduced shivering and some spontaneous movements. Removal of the fastigium increased extensor rigidity and replaced all repetitive responses (except lapping and swallowing) by postures maintained during stimulation and followed by rebound. Subsequent destruction of the vestibular complex abolished extensor tonus and permitted reevocation of rhythmic movement.

Varying the parameters of stimulation has showed that the central nervous system exerts a filter-like action. Wyss (66) has extended his observations on the afferent vagus to monkey and found that low intensity, low frequency stimulation gave inspiration (though rather weaker than in cats, dogs and rabbits) and high-frequency or high intensity, strong expiration. Delgado, Fulton & Livingston (67) found a similar effect on respiration from area 13, albeit unsustained. Uvnas (68) reported that 60 per sec. stimulation of the rostral diencephalon caused bladder relaxation and 3.5 per sec. bladder contraction. Bailey (69) has observed that stimulation of the face subdivision in area 4 with 12 per sec. or higher frequencies affects muscles innervated by the seventh nerve, whereas with 10 per sec. or less it affects only muscles supplied by the twelfth. Chusid (78) stimulated area 8 at 40 per sec. and found the usual deviation of eyes to the opposite side, but when he raised the frequency to 400 per sec. the eyes snapped back to the centre. Our present Aristophanic notions of half-centres must be modified accordingly.

Fifth order arc.—Research on cortex is now of two types. One, concerned with interdependence of gross structures, discovers new

areas and tracts, providing raw data for the other which, dealing with fine nets, resolves the action of histologically uniform regions. Studies in fine anatomy supplement the former, giving the order and multitude of neuronal connections. A new technique is required to give the lengths and comparative populations of open long-chain and closed reiterative circuits and so test experimentally Pitts' theory on the course of excitation through a net randomly connected in the fine but statistically ordered in the large.

Morison & Bassett (70), continuing the studies on rhythmicity in cat thalamus, report that although bursts of 8 to 12 per sec. continued as long as three days after decortication, they disappeared thereafter, possibly due to degeneration of the nucleus centralis lateralis. Further study of thalamocortical relations reveal that limbic cortex may contain a mechanism for autonomic regulation, confirming the physiological observations made by Smith (71). Rose, Woolsey & Jarcho (72) state that the anteromedial nucleus projects to anterior limbus, and anteroventral and -dorsal nuclei to the retrosplenial region. Electrical stimulation of the mammillary bodies produced response at areas 23 and 29 in monkeys and at the retrosplenial region with occasional relays to anterior limbus in cats. Ward & McCulloch (73) have demonstrated discrete projections from 6a to the mammillary nuclei, and lateral and posterior hypothalamic regions. The orbital surface 47, 10, and 53 fired the paraventricular nucleus, and 45 and 47 the posterior hypothalamic area. Bilateral ablation of 13 by Fulton, Livingston & Davis (74) more than quadrupled preoperative activity where stimulation produced a condition resembling sleep; and this may be related on the one hand to the hypoactivity Bailey found with temporal lobotomy (since the orbital surface projects to the anterior pole of temporal lobe) and on the other to the sleep mechanisms discussed by Nauta (75). Rose & Woolsey (76), using wholesale ablations, also report that the paraventricular and habenular complexes as well as the pretectal group are independent of telencephalon whereas all elements in dorsal thalamus and the reticular complex in ventral thalamus degenerate entirely after deprived of higher structures. Some of these dependent elements may be related to subcortical telencephalic groups.

One of the major discoveries in the past few years has been that of double representation of touch, sound, and sight in the cortex. Sugar, French & Chusid (77 to 80) have complemented the

second sensory area on the inferoparietal plane with an adjacent second motor strip. Both are reciprocally connected bilaterally with pre- and postcentral cortex, the posterior portion to leg and shoulder and anterior portion to thumb and face areas on the primary strip, and homiotopically to the contralateral inferoparietal plane (81, 82). Woolsey (83) has already mentioned that Sensory II projects to paramedian lobule.

Woolsey, Chang & Bard (84) suggest that afferent impulses to the cord terminate in a definite way in relation to the pattern of representation in motor areas. Woolsey & Chang (85) have shown the cortical origin of pyramidal tract by antidromic volleys from the medullary pyramids. It includes Brodmann's area 6, 4, 3, 1, 2, 5, and 7 in monkey, both components of response best developed in 4 but almost as large in the postcentral gyrus. This may explain in part why Ades & Raab (86) found almost complete recovery of motor function following two-stage bilateral ablation of 4, but marked paresis if 3, 1, and 2 were included in the lesion. Magoun listed the motor changes in monkeys with internal capsule lesions. Unilateral section of one or both limbs produced to lesser or greater degree initial atonia and areflexia with loss of voluntary movement most marked in the lower leg and decreasing rostrally. Thereafter, voluntary control returned most rapidly for gross movements, never entirely for fine. Bilateral lesions gave marked rigidity and spasticity with slow return of voluntary movement and coarse effort tremor. Welch & Kennard (87) report tremor also as a result of ablating areas 6 and 4-s. It was associated then with spasticity in flexion.

Sperry (88) criss-crossed the cortex with a knife, penetrating through into the white matter and found no impairment of motor function or sensorimotor integration after the first month. The organization seems to be primarily vertical as would be suspected from histology—not horizontal as proponents of "field" theories have proposed.

Two interesting reports on area 4 have been issued several years apart. J. Ward (89) had discovered that the response from stimulating one point on the cortex varied with the position of the animal in space. Then Chang, Ruch & A. A. Ward (90) found that, with position frozen, such consistent fine responses could be elicited that separate muscles could be mapped on 4. Both these findings were coordinated by McCulloch (91) in his review on functional

organization of cerebral cortex. Briefly his notion was that incoming impulses to the cortex fan out, and, scanned by an energizing sweep perhaps originating in the undifferentiated thalamic nuclei, go through all the transformations of a set; the resultants being then summed and averaged are then invariants. The universals so derived are relayed to association areas where further abstracted, or else directly to motor regions to excite resonant groups of cells. Such a theory for vision and optokinetic reflexes by Pitts & McCulloch (64) provides a physiological mechanism for Gestalten and a statement of the internal economy of certain reflex nets. Somatic sensibility clearly submits to similar treatment.

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VISION

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An enormous volume of literature on vision has become available since the last review (1) and the author makes no pretense of having abstracted all of it nor of having selected without bias. The present review covers the literature from September 1944 through June 1947, although it includes a few earlier studies which have not been previously reviewed.

Reviews and Bibliographies

A number of good reviews and bibliographies on selected topics in vision have become available recently. Of general interest, however, is the classified bibliography of visual literature for the period 1939 through 1944 by Fulton *et al.* (2). This bibliography contains over thirty-four hundred titles. Spiegel's handbook (3) contains two relevant chapters, one by Bartley (4) on "Vision," and the other by Bender (5) on "Ophthalmoneurology." Both stress neurophysiological aspects of the visual process and cover the literature for the year 1945. Two texts, Lyle (6) and Spiegel & Sommer (7), are also concerned with the neurology of vision, but place more emphasis on pathology than on normal vision. The first volume of Gates' text (8) contains a good summary and extensive bibliography on the inheritance of color blindness, myopia, night blindness, and many other types of visual defects. Two articles (9, 10) and a book (11) on light and seeing deserve mention, in spite of their orientation toward problems of illuminating engineering. All three summarize a large number of basic researches on the relations between visual acuity, contrast, brightness, time of exposure, and glare. Finally, Glasser's handbook (12) contains a number of comprehensive reviews which are relevant. Several of these are mentioned later.

Physiology of Vision

Photochemistry of the retina.—It has been known for some time that rhodopsin (visual purple) first turns orange (transient orange) before it bleaches to retinene (visual yellow). It is also known

now that a mixture of phospholipids is associated with rhodopsin in the retinal rods and that the exposure of dark-adapted retinae to light liberates retinene and a large amount of phospholipids (13). Two of these lipids, both colored and one corresponding to transient orange, have been extracted from bovine retinae by Krause (14). He has been able to isolate enough of these two lipids, provisual red (transient orange) and visual red, to permit a partial analysis of their structures. Some idea of the magnitude of his work, and of the difficulty of conducting research on the photochemistry of the retina, may be conveyed by the statement that the "yield was about 80 mgm. of visual red and 60 mgm. of yellow pigment for each batch of 10,000 eyes"!

Earlier evidence for a correlation between the acetylcholine content of the retina and retinal sensitivity had been contradictory. Additional negative data come from a study by Easton (15) who finds no differences in the acetylcholine content of light- and dark-adapted frog retinae.

The search for a photosensitive pigment for cone vision has always been a matter of great interest. Although a number of such pigments have been reported, their existence has been open to question. Researches by Bliss (16, 17, 18) confirm the existence of only one of these, iodopsin, discovered earlier by Wald in chicken eyes. Iodopsin has a spectrum of bleaching effectiveness which resembles the sensitivity of human cones with a maximum at 560 mμ. This work is a significant advance in our knowledge of the chemistry of daylight vision.

Experiments and theoretical formulations continue to explore the photochemical theory (19 to 30) and new equations have been suggested to fit visual acuity, flicker, brightness discrimination, and dark adaptation data. Although the new equations fit these data better, it is still doubtful that this curve-fitting approach tells us much about the mechanism of the retina (31).

There are three new reviews in this field, two by Wald (32) and Granit (33) on the photochemistry of vision, and the other by Hahn (34) on the role of seven vitamins in the physiology of vision. The latter article is not limited to the chemistry of the retina, however, since it also shows the function of the vitamins in preserving the normal physiology of the cornea, retinal nerve tissues, and vascular supply.

Electrophysiology of the retina.—The application of electro-

retinographic (ERG) techniques to the clinical diagnosis of ophthalmic defects in man is the subject of a monograph by Karpe (35). Much of his work has been concerned with the development of standardized testing and recording procedures and with the investigation of artifacts in ERG records. Rod and cone components in ERG records have been reported by Adrian (36, 37). Experiments on infrahuman subjects with predominantly rod or cone retinae give results consistent with human data (38).

The excitability of single sense cells in Limulus as a function of various adapting illuminations and changes in light intensity has been studied by Riggs & Graham (39). Several papers have been published in this field by Granit (40 to 44), but these are all overshadowed by the appearance of his long-awaited book (33). During the last twenty years, Granit's contributions to the neurophysiology of vision and his theory of color vision have made a profound impression. The reviewer predicts that this book will, too. It is a scholarly work, impossible to review in a few words. Four sections deal with (*a*) the electrical response of the retina and optic nerve; (*b*) the electrophysiological responses of the rods and cones; (*c*) the photosensitive substances of the retina and the mechanism of excitation; and (*d*) the neurophysiology of color vision and Granit's theory of color vision.

Color vision and color blindness.—A group of extremely interesting studies has been concerned with blue and violet vision (45 to 48) and with the perception of small colored stimuli. Willmer (49) has confirmed his earlier reports that the fovea is dichromatic and tritanopic by showing that curves of luminosity, color-mixture and hue-discrimination obtained in the fovea are characteristic of tritanopic vision. This is not a new finding, since Konig discovered it about fifty years ago. The phenomenon was apparently ignored in the intervening years and Willmer's rediscovery of it has stimulated a number of lively communications (50 to 53). This matter is not settled definitely, however, because other data still show the operation of blue and green receptors in the fovea (54). This discrepancy may possibly be due to a difference in the sizes of stimuli used—1° for Stiles (54) and 20′ for Willmer (49). In any case, Willmer's data and theory of color vision are now summarized in a book (55) which is intriguing because of its novel interpretation of existing data. In essence, he argues that color vision is mediated by the cones and two types of

rods. The admission of another type of rod is a retreat from his earlier view, but the theory is still unique in postulating fewer recipient elements than are required by the Young-Helmholtz theory.

Hartridge (56) claims that Willmer's findings are true of extrafoveal regions if the stimuli are small enough. He reports (57, 58, 59) that when colored stimuli are reduced in size, red and blue become gray or black, while yellow and green become white—the "antichromatic response" (60). He believes that it accounts for the lack of colored fringes which we should expect to see because of the chromatic aberration of the eye.

In still other experiments (61, 62, 63) a very small spot of white light was focussed on the retina and allowed to move slowly over it. In some places the spot appeared red, and in other places orange, green, pale blue-green, grey-blue, or white. Tests with other colors lead Hartridge to conclude that there are a number of color receptors in the retina and that receptors of similar, or nearly similar, response characteristics are located in groups or clusters. He has even been able to construct a plan showing the approximate positions of the red, blue, and green receptors in his own left fovea (64). This technique parallels Granit's microelectrode method of exploring the retina and the correspondence between the findings of the two investigators is striking. Discrepancies between the two halves of a small photometric field used in measuring hue discrimination as a function of wavelength have been reported by Thomson (65). If all the above findings on the colors of small objects were to account for Thomson's data, it would probably be necessary to postulate areal effects which are a continuous function of wavelength.

Other studies contain data and arguments to support any of a number of color theories. The three basic sensation curves have been determined by means of a new technique (66) and additional data suggest that each of the three color-sensitive mechanisms has its own intensity discrimination and visual acuity characteristics (67). Two mathematicotheoretical studies (68, 69) show how the three sensation curves can be integrated with the facts of color blindness, and a third study of this type (70) exploits Troland's modulation theory of color vision. Judd feels that his work (69) supports a three-component color theory and that it is consistent with the dominator-modulator theory proposed by

Granit (33). On the basis of several lines of evidence Hartridge (71) concludes that a triple-cone theory of trichromatic vision is more tenable than a single-cone theory. Pickford (72), on the other hand, presents data which strongly support a four-color theory. His factor analysis of a large amount of color vision data from normal subjects yields three factors: (*a*) a general "testing" factor; (*b*) a bipolar red-green factor; and (*c*) a bipolar yellow-blue factor. A similar analysis of data on thirty-eight red-green blind subjects yields the following factors: (*a*) general; (*b*) bipolar—yellow-blue; and (*c*) inadequate evidence of a third factor. Other analyses of this sort are also presented in this same paper. Most color theories have difficulty in explaining the abnormal visibility curves of protanopes and the essentially normal visibility curves of deuteranopes. Jahn (73) has attempted to solve this difficulty with a neural explanation. His theory states that most of the fibers in the optic nerve are connected through multisynaptic ganglion cells and bipolar neurones to rods and cones; others, fewer in number, are connected through midget ganglion and bipolar cells to single cones. In protanopia, the red cones in both types of connections are nonfunctional; in deuteranopia, only the latter connections are nonfunctional.

More information about basic differences in retinal sensitivity between the color-normal and color-anomalous eye has come from two sources. Hecht & Hsia (74) measured foveal thresholds at five spectral points for six normal subjects, six deuteranopes and four protanopes. They find slight increases in the thresholds of the deuteranopes, especially in the green. Foveal thresholds for the protanopes are normal in the violet region but diverge increasingly toward the red. At 651 mμ the discrepancy is very large and amounts to 1.12 log units. These findings are in good agreement with the data of Chapanis (75, 76, 77), when allowance is made for the different test conditions, and relative crudity of the dark adaptation measurements employed by the latter. Both sets of data indicate that the traditional employment of relative visibility curves has masked for many years an important difference between the photopic sensitivities of the normal and color-anomalous. This also appears to be the essential point of de Vries' study (78) but his data are plotted relative to luminosity at 650 mμ so that this finding is not as clear cut as in the experiments mentioned above.

In a somewhat different vein, the examination of 16,180 RAF candidates has shown 6.63 per cent of them to be color defective (79), and there appears to be a small, but significant, correlation between color blindness and eye color (80, 81, 82). This tendency is more pronounced for the milder, anomalous defects. Ethnic data, however, contradict these findings. East Indians are more highly pigmented, and New Zealanders less highly pigmented, than Fijians. Yet the incidence of color deficiency among Fijians (0.8 per cent) is much less than among the other two groups (8.1 and 6.0 per cent, respectively) (83). There may still be such a correlation within any one racial group and these studies suggest an interesting hypothesis for further investigation.

Reports of the improvement of color blindness by training (84 to 88), and the administration of vitamin A and cobra venom (89, 90, 91) still continue but not without criticism (92 to 95). During this time there has been only one carefully controlled study on the effectiveness of vitamin A in improving color vision (96). The results were negative. Many of Dvorine's color vision training plates (97) are arranged in series, graded in difficulty, but with identical numbers appearing on the plates in each series. It is unfortunate that the ability to memorize charts should be confused with improvement in color vision. Those of us who have been in the service have seen many color-blind individuals who had once been "cured." Evidently a comprehensive treatment of these problems is still needed to settle the matter once and for all.

Dark adaptation and night vision.—Work in this area has made it increasingly apparent that dark adaptation and night vision are not synonymous. Seeing at night (night vision) is a complex perceptual task involving dark adaptation, form discrimination at low illuminations, training, experience, and other factors (98, 99, 100). The independence of form or pattern vision and light perception or dark adaptation is especially pronounced in cases of strabismic amblyopia (101), although unfortunately it is not clear whether form vision at both photopic and scotopic levels of illumination is affected. This situation has had a salutary effect in stimulating research on aspects of scotopic vision other than dark adaptation. Thus, the characteristics of peripheral visual and motion acuity under scotopic conditions (102 to 105) and the scotopic visual field (99, 106, 107) have now been investigated in some detail. Emphasis on the experience factor in seeing at night

is reflected in the development of several night vision trainers (108 to 111) for the armed services, but there appear to be no controlled studies to show how effective these training programs really were.

Other studies on dark adaptation have, for the most part, shown small effects due to a number of different variables. There are now additional data to show an increase in rod threshold with advancing age (112, 113). The use of paredrine produces a small but significant improvement on night vision tests (114). Repeated or prolonged exposures to sunlight (115, 116) and ultraviolet light (117, 118, 119), on the other hand, impair dark adaptation a small, but significant, amount. Ultraviolet light affects only the rods, however (119, 120, 121). Small wave-like fluctuations, of irregular amplitude, and with a period of three to seven minutes have been reported in dark adaptation records (122, 123).

Lowry's (124) earlier claim that the color per se of a preadapting light has no effect on subsequent dark adaptation was vigorously attacked in two experimental papers (125, 126). They show that when red and white lights, equated for brightness in photopic vision, are used, dark adaptation is faster following exposure to red than following white. These findings are in agreement with another study on the time required to see dimly illuminated objects following exposures to lights of various colors (127). Had Lowry been correct, it would have been embarrassing to many individuals who advocated the use of red light in military applications (128, 129, 130, for example).

Russian experiments continue to show improvement in night vision due to intersensory stimulation (131, 132, 133). Results with auditory, olfactory, gustatory, labyrinthine, thermal, pain, tactile, proprioceptive, and interoceptive stimuli show "that excitation of any receptor produces changes in the sensitivity of the dark-adapted eye." The extravagant claims and scanty data in these reports emphasize the need for an independent check on such intersensory facilitation.

Because of the large numbers of men who were given night vision tests during the war, it is not surprising to find cases of night blindness described in the literature. Hinn & Montano (134) report one, Chapanis & Rouse (135) three, and Rowland & Sloan (136) ten cases. Parker (137) studied thirty-nine men who complained of night blindness. Of these, only nine were found to have

impaired dark adaptation. Five were malingerers, eleven showed normal dark adaptation, and fourteen were psychoneurotics who were helped by psychotherapy. Holmes (100) found that the night vision of 217 students of Japanese ancestry was significantly poorer than the night vision of Caucasian students. Additional data, however, show that the difference might be due to any of a number of factors. Although these studies do not contribute much to our understanding of night blindness, they emphasize the complex nature of the seeing mechanism. The causes of night blindness may be varied and administration of massive doses of vitamins does not always produce improvement.

The Purkinje shift of maximum sensitivity from 560 mμ in bright light to 505 mμ in dim light produces a relative myopia in scotopic vision of about 0.4 diopters because of the chromatic aberration of the eye (138, 139). More important, however, is the discovery that in scotopic vision the eye is essentially a fixed focus instrument (139). This finding should influence many applied problems of night vision.

Luminosity functions of the eye.—The development of near infrared viewing devices and the use of ultraviolet light for military purposes provided the impetus for important research on the spectral sensitivity of the eye. Wald *et al.* (140, 141) have extended the luminosity function of the eye, both foveally and peripherally, to 1050 mμ. The fovea and periphery are about equally sensitive at 685 mμ, but at longer wavelengths the periphery becomes considerably more sensitive than the fovea. Foveal and peripheral measurements on fifty-four subjects with light of 685, 725, 835 and 873 mμ also show the extent of individual differences in sensitivity to the near infrared. Related studies provide data on average scotopic visibility from 300 to 800 mμ (142), on average photopic visibility from 300 to 950 mμ (143, 144, 145), and on scotopic sensitivity at 365 and 546 mμ (146). Wald (147) has also measured spectral sensitivity between 365 and 750 mμ, centrally and peripherally, in normal and aphakic eyes. His measurements enabled him to derive curves for the absorption spectrum of the macular pigment and the optical density of the lens of the eye. In 1944, Stiles & Smith (148) computed a mean scotopic visibility curve on the basis of data available at that time. This work should now be extended to include the new data on these functions.

Anoxia, carbon monoxide, and hyperventilation.—A number of

studies continue to emphasize that visual functions are among the first to show impairment due to anoxia. Acute anoxia has been shown to affect the peripheral blind areas (angioscotoma) and visual field (99, 149), dark adaptation (150, 151), critical flicker frequency (152, 153), contrast sensitivity (154, 155), vernier and stereo acuity (156), heterophoria (157), and brightness discrimination (158, 159). Some of these effects are noticeable at altitudes as low as 8,000 feet (158). Impairment in the dynamic visual field has also been found to occur with chronic intermittent anoxia at low altitudes (10,000 feet) (160, 161). These decrements are not the result of psychological factors—lack of attention or motivation—but are attributed to actual impairment of the neurons of the retinogeniculostriate system (162). The decline in critical fusion frequency with anoxia is accompanied by changes in electroencephalographic recordings; degrees of anoxia which do not alter the critical fusion frequency have no effect on the electroencephalogram.

Further evidence on the exact mechanism of this impairment comes from a study which shows that the effects of anoxia on brightness discrimination may be mitigated by the ingestion of glucose (163). The "antianoxic" effect of glucose appears to be due to its direct action on the rate of oxidation in the central nervous system. Confirmation of this hypothesis comes from the fact that insulin hypoglycemia also impairs brightness discrimination and that this decrement can be largely overcome by the inhalation of 100 per cent oxygen (164).

Other studies show that hyperventilation affects both stereo and vernier acuity (165) and contrast discrimination (166). The data on the effects of carbon monoxide are contradictory in one respect. McFarland *et al.* (167) find that the effects of anoxia and carbon monoxide on brightness discrimination are cumulative. A related study by Lilienthal *et al.* (153) shows that the critical fusion frequency is impaired by mild anoxia (9,000 to 12,000 feet) and that increments in carboxyhemoglobin of 5 to 10 per cent result in deterioration at much lower altitudes (5,000 and 6,000 feet) where anoxia alone has no effect. In experiments by Vollmer *et al.* (168), however, the inhalation of carbon monoxide during anoxia did not produce any additional impairment of the critical fusion frequency threshold or visual field. The final perplexing study in this area shows that concentrations of methemoglobin up

to 30 per cent in the blood show no increased effect on dark adaptation either at sea level or at altitudes of 12,000 and 18,000 feet (169). The answer to these conflicting results may lie in the way the oxygen dissociation curve of the blood is affected by carbon monoxide and methemoglobin, but present data can only suggest the answer.

Effects of smoking.—Three studies indicate adverse effects of smoking on vision but disagree as to the cause. McFarland *et al.* (167) found that smoking three cigarettes increased the carboxyhemoglobin saturation of the blood by 4 per cent with a consequent loss in brightness discrimination. When the subject did not inhale, smoking did not increase the blood carboxyhemoglobin and had no effect on vision. Since the nicotine absorption in the latter case is 60 per cent as great as in the former, the authors feel that only the carbon monoxide is responsible for the visual decrement. Sheard (170), on the other hand, finds that dark adaptation is impaired by smoking two cigarettes, whether or not the smoke is inhaled. Cigarettes containing no nicotine do not produce the effect. He feels, therefore, that the loss is due "largely if not wholly to nicotine." Further, the size of the angioscotoma has also been shown to increase following the smoking of one cigarette (171). Since cigarettes containing one-tenth the nicotine content produce a much smaller effect, the results of this study agree with Sheard's.

From the clinical literature comes evidence that patients with restricted visual fields and impaired visual acuity due to tobacco-alcohol amblyopia can be improved by increasing their vitamin B intakes with unabated use of tobacco, alcohol, or both (172, 173). This seems to indicate a general disturbance of metabolism with damage to the neurones of the optic system. It would be interesting to know definitely if the cause of these fairly permanent effects is related to that of the transient effects of smoking found above.

Miscellaneous studies.—Probably one of the largest studies of vision ever to have been reported is the one by Blackwell (174, 175, 176) on the contrast sensitivity of the normal eye. In all, more than two million responses were recorded. Contrast thresholds are presented for stimuli brighter and darker than their background and for two values of stimulus exposure. In each case, wide variations were studied in the parameters: stimulus contrast, stimulus area, and adaptation brightness. Other measurements of visual acuity over a wide range of sizes, brightnesses, and brightness

contrasts (177), and of visual thresholds for point sources in fields of brightness from dark to daylight (178), have also been reported. These studies contribute important basic data on the functioning of the normal eye.

The perception of fine detail is the subject of a monograph by Hartridge (59). He attempts to provide an answer to the problem of why the eye can perceive such fine detail when its lens system is known to contain a considerable amount of chromatic aberration. [Hecht *et al.* (179), for example, have found that a wire may be seen against a sky of high brightness when its diameter subtends only half a second of visual angle!] Hartridge's experiments extend over many years and have led him into investigations of the colors of small objects. His findings in this area have already been discussed and it is likely that this monograph will stimulate still further research on this general problem.

Difficult to classify are experiments by Kravkov & Galochkina (180, 181, 182). They report an increase in foveal sensitivity to lights shorter than 570 mμ, and a decrease in sensitivity to lights longer than 570 mμ, when a constant current of 0.02 ma. is allowed to pass through the eye with the positive electrode in contact with the eyeball. Reversing electrodes produces opposite effects. They feel that these results can be accounted for by alterations in potassium and calcium ion concentrations produced by the electric current. They support this view by showing (182, 183) that injection of calcium into the eyeball increases the foveal sensitivity of the eye to green light and reduces sensitivity to red light. Potassium has the opposite effect.

Visual Examination and Testing

The importance of the visual sense to men in combat resulted in an enormous amount of work to select individuals with excellent visual capacities for various types of military jobs. A review of the period cannot ignore this voluminous literature in spite of its applied nature. It represented, in many ways, a confused research effort. Disregard of important physiological and psychological variables, ignorance of related investigations in other laboratories, inadequate sampling, poor statistical treatment of data, and hasty generalizations characterize much of this work. (It is not all cited here.) Also contributing to the general confusion was a lack of agreement on the aim of all this testing: should the tests merely

eliminate deviant individuals, or should they be capable of grading visual capacity reliably and validly?

Statistics continued to show a large incidence of visual defects (5.8 and 9.5 per cent) among young healthy males (184, 185), and the incidence among unselected men is undoubtedly much greater. This fact plus the cost of the testing programs may have been partly responsible for two important research trends in this field: (*a*) the examination of the selection standards used by the armed services to discover whether these standards are valid and necessary, and (*b*) the critical evaluation of the visual tests themselves to determine whether they give consistent results and measure what they purport to measure. The last two properties are called the reliability and validity of a test and have been investigated for many years in standardizing psychological tests. The introduction of these concepts and techniques into the field of visual testing has shown in several cases that visual tests which had been accepted at face value give results which (*a*) are quite variable from one test occasion to the next, i.e., they have a large error of measurement; (*b*) bear little or no relation to other tests which are supposed to measure the same visual function; and (*c*) bear little or no relation to success or failure in the practical jobs of flying, seeing at night, or using a lathe. The use of these techniques has already resulted in the refinement of many tests and test procedures.

Although most of this work has been done in three fields, these critical inquiries have been addressed to many types of clinical tests of vision—the phoria, visual acuity, and depth perception tests (186 to 199), for example. It is likely that this applied research will be supported in the future since reports continue to show that certain types of visual defects are related to accident-proneness and productivity in industry (200 to 203). The three areas of intensive research are discussed separately below.

Color vision and color blindness.—Several new tests of color vision appeared during the war years. The first volume of Dvorine's two-volume set of charts (204) is a test similar to the Ishihara. Dvorine's test is interesting only in that he uses more types of color combinations than appear in the Ishihara and American Optical Company (AO) plates. There seem to be no data on his test and, superficially at least, it contains several faulty design features found in the first edition of the AO plates. The Boström-Kugelberg plates (205) are rather unique in design and appear to have over-

come some of the difficulties—ease of memorization, faulty numeral design, etc.—which characterize many tests of this sort. Test makers will certainly profit from a careful study of this one.

New and improved instrument tests of color vision have also been described. Sloan (206), for example, showed how the Eastman color temperature meter can be used as a simple anomaloscope. She has also developed a quantitative test of color vision by varying systematically the brightness of the test lights in her lantern (207, 208). Extensive data attest to the reliability and validity of her device. Farnsworth (209) analyzed the principles to be followed in designing color vision lanterns and constructed an instrument (210) on the basis of these principles. Results from over two thousand tests indicate that it has the advantages and few of the deficiencies of older lanterns. The monochromatic colorimeter designed by Van den Akker *et al.* (211) is primarily a research instrument although it might also be used as a test. Finally, Dimmick (212) describes a quantitative test of color vision developed by the Inter-Society Color Council. The amount of defect is assayed in terms of the number of confusions made by the examinee in matching forty colored chips identical in hue but varying in saturation. There has long been a need for a test which will yield quantitative measures of color defect in terms of some logical dimension of the visual stimulus. Recent developments in this field are encouraging.

Most of the work on color vision testing has been concerned with a critical evaluation of existing tests, test construction, and methods of testing. New statistical criteria for selecting test plates have been suggested by Green & Sloan (213) and the important variables to be considered in testing color vision and in constructing color vision tests are summarized in two excellent reviews (214, 215). Both of the latter papers also survey types of color vision tests now in existence. The importance of the quality of the illumination in testing color vision has again been demonstrated (216, 217).

A number of studies (218 to 226) have compared existing chart tests. In general, it appears that the Rabkin test is the best of these (222) and the Ishihara next (220). The first edition of the AO plates contained a number of defects and the second edition appears to be only slightly better (218, 224, 225, 226). Abridged versions of the AO test to eliminate certain defective plates have

been suggested (227, 228). All of these chart tests (with the possible exception of the Rabkin) give dichotomous classifications. Properly administered, they can be useful screening tests.

A few studies have attempted to validate color vision test results against realistic criteria. Studies by Sloan (225)[1] have shown that color deficient individuals have difficulty with many standard types of colored signals used by the Army Air Forces. Similar data show that the color defective have great difficulty with certain types of small Navy signal lights (229, 230).

Dark adaptation and night vision.—The large number of tactical operations carried out at night during the war made the armed services acutely aware of individual differences in night visual capacity. Army, Navy, and university laboratories responded to this situation with an astonishing array of "night vision" tests. Tests of dark adaptation, form discrimination at low illuminations, contrast sensitivity, glare recovery, and many others were constructed and used (231 to 261).[2] This test program appears to have been less well integrated than others and the Army Air Forces, for example, wrote into its regulations (AR 40–110, 12 April 1945) that night vision tests could be administered with any one of four instruments although data from its own laboratories showed that scores on two of these tests showed virtually no relationship to each other or the other two tests (234).

If any positive conclusions can be drawn from this welter, they are these: (*a*) it is easier merely to select night-blind individuals than to grade night visual capacity reliably (250); (*b*) in general, dark adaptation tests are not the best predictors of ability to see at night. Best results seem to have been obtained with those tests which measure visual acuity or form discrimination at low illuminations (234). It is unfortunate that the review of this literature must end with the familiar statement: more work is needed on these problems. Holmes (238) and Rowland (250) elaborate on this situation and the former describes a thorough, systematic

[1] Her paper is an excellent summary of the color vision testing program carried out at the AAF School of Aviation Medicine during the war. It lists a number of unpublished reports not cited separately in this review.

[2] The report by Rowland (250) contains a good summary of the night vision research program at the AAF School of Aviation Medicine from January 1942 to June 1945. It also contains a complete bibliography of unpublished reports which are not cited separately here.

series of examinations for assessing night vision. The completion of it would yield some sorely-needed information.

Stereoscopic vision.—A war-born problem was the visual selection of operators for stereoscopic range and height finders. As in the case of night vision testing, a large number of tests was tried (262 to 279) but this program of research appears to have met with a little more success than did the night vision program. Two factors appear to account for the difference: (*a*) the ultimate criterion to be met was more precise and easily measured in the case of the stereofinder operators, success or failure in ability to use these instruments being objective and easy to assay; and (*b*) unlike the night vision testers, investigators in this field did not settle upon a single test of stereo vision. Batteries of tests which measured interpupillary distance, visual acuity, the phorias, stereo acuity and aniseikonia were ultimately used in selecting men for stereofinder operation. The broad approach appears to have produced better results.

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DIGESTIVE SYSTEM[1]

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Mouth

A permanent record of the superficial appearance of the anterior third of the tongue can be obtained by painting the surface with a solution of Evans blue in gum acacia and taking an impress on glazed paper. The prints are examined under a low power objective. An examination of ninety-nine normal young males gave an average of 52.5 per cent filiform and 8.1 per cent fungiform papillae. Dietary deficiencies reduced the number of filiform papillae. Fissures and creases are also recorded (1). Lewinsky & Stewart (2) have studied the innervation of the epithelium of the gum in the sheep, mole, rabbit, rat, mouse, ferret, and man. In the human gum three intrapapillary endings and four types of intraepithelial nerve fibres are described and illustrated. Histological evidence suggests that the distal portions of the intraepithelial nerves undergo degeneration with the shedding of the epithelial cells and that new end organs are formed from the viable part which advances with the newly formed epithelial cells. Dissolution of dental substance has been reported in subjects who suck lemons or have taken interval feedings of lemon juice in water therapeutically (3). The ten essential amino acids and glycine are present in human saliva (4). Chewing a paraffin block in which was incorporated 7.5 mg. sodium hydrogen sulphite gave a saliva which on incubation showed a marked decrease in acid production in comparison with paraffin stimulated saliva (5). In the chloralose cat, β-dimethylaminoethylbenzhydryl ether hydrochloride in doses of 2 to 10 mg. per kg. body weight depressed salivary secretion induced by acetylcholine or pilocarpine, or by stimulation of the chorda or cervical sympathetic (6). In 54 normals the serum amylase was about 325 "units"; in 265 cases of mumps more than 83 per cent had a serum amylase above 400 "units" in the first week. The rise in serum

[1] This review covers the period from June, 1946 to June, 1947.

[2] I am indebted to Miss J. Emmett for valuable assistance in compiling of references and in abstracting some of the material.

amylase followed the evolution of the parotitis and, as shown by the co-existent normal serum lipase values, was of extrapancreatic origin. The appearance of orchitis and epididymitis did not affect the serum amylase values. The determination of the serum amylase is regarded as of value in the differential diagnosis of parotitis (7). Mayer-Gross & Walker (8) have reported 203 taste tests in a hundred subjects undergoing Sakel's insulin therapy for early schizophrenia. The subjects were offered five drinks to taste, 30 per cent sucrose, saccharine to the same sweetness intensity, 5 per cent sucrose, isotonic saline, and water. When the blood sugar level fell below 50 mg. per cent the concentrated sucrose solution was preferred.

Esophagus

Mann and his colleagues (9) have investigated the effect of a double vagotomy at different levels in trained adult dogs. Section of the nerves at or above the hilum of the lungs produced paralysis and dilatation of the distal moiety of the esophagus. There was no impairment of appetite but the animals showed a pronounced tendency to emesis. Swallowing thrust the meal into the dilated esophagus but tonic contraction of the smooth muscle forced part of the bolus into the pharynx from which it was promptly vomited. In half the animals the cardia was distinctly patulous. After supradiaphragmatic vagotomy a normal esophageal activity to the swallowing of a bolus of food was observed but after a brief interval the food was regurgitated into the esophagus. This is attributed to an impairment of the receptive relaxation of the stomach associated with a hypotonic cardia. Similar results were obtained when vagotomy was performed on sympathectomised animals. The vagal supply to the cardia is considered to be chiefly motor in function. Grimson *et al.* (10) could observe no dysphagia or abnormal function of the esophagus in forty nine subjects on whom a subtotal or total paravertebral sympathectomy had been performed some seven to sixty-six months previously or in twenty-seven subjects who had had a vagotomy at the lower end of the esophagus for two to nineteen months. The Plummer-Vinson syndrome has been attributed to a nutritional, possibly B-vitamin deficiency since it is associated with esophageal muscle degeneration, diverticuli, dysphagia, rhagades, a smooth papillae-free tongue and anaemia (11). Stimulation of the vagus in the neck or reflex stimulation of liver, gallbladder, stomach wall, and the

peritoneum of the upper abdomen in dogs caused a shortening of the esophagus with the production of esophageal hiatus hernia. This reflex shortening of the esophagus was abolished by atropine or vagotomy (12). Barrett (13) has reviewed the literature and described three new cases of spontaneous perforation of the esophagus. Allison (14) and Rienhoff (15) have described the technique for esophagojejunostomy for irremovable carcinoma of the cardia. The reconstruction of the esophagus by a skin-lined tube is described by Stevenson (16). Prostigmine bromide, 5 mg. tablets *per os*, is stated to have caused complete relief in twenty cases of heart burn in pregnancy (17).

Stomach

Kenamore (18) removed a bobby pin from the stomach of a four year old child by means of an alnico magnet attached to a stomach tube.

Davies (19) has studied the secretion of hydrochloric acid in a closed tube of isolated frog's gastric mucosa suspended in a Warburg cup, in frog saline, gassed with 95 per cent oxygen and 5 per cent carbon dioxide at 25°C. Autumn, winter, and early spring frogs showed no spontaneous acid secretion, but acid secretion accompanied by an increased overall uptake of gas and an equivalent increase in the bicarbonate concentration in the surrounding medium was obtained after the addition of histamine to 1 mg. per cent. It was calculated that the carbonic anhydrase present in oxyntic cells was needed to accelerate the absorption of carbon dioxide to neutralise the alkali formed. When the histamine-activated mucosa was kept in bicarbonate-saline the acid produced varied between 0 and 0.1N and the Q_{HCl} sometimes reached twice the Q_{O_2} without causing visible damage to the tissue; in phosphate-saline when the Q_{HCl} exceeded the Q_{O_2}, tissue disintegration and perforations occurred but histamine-resistant mucosae were never ulcerated (20). In autumn and early spring frogs' gastric mucosa a potential difference of thirty to fifty millivolts occurred across the membrane, which decreased during the secretion of hydrochloric acid. Under anaerobic conditions both potential difference and acid secretion were abolished (21).

In anaesthetised dogs, Rehm (22) found that the e.m.f. responsible for the potential difference originated between the mucosa and the submucosa. The same author with Hokin (23) has observed the

gastric potentials and acid secretion in the greater curvature of the dog's stomach after injection of 0.1 to 1.0 mg. mecholyl or 5 to 10 mg. pilocarpine hydrochloride subcutaneously every ten minutes and finally after atropinisation. With the onset of secretion the potential difference fell but if the rate of secretion was less than 0.4 mg. hydrochloric acid per 10 min. the fall was not as great as usual and the potential difference levelled off at a higher value. Atropine inhibited secretion and concomitantly restored the potential difference to its resting value. Ethanol in isotonic saline caused a fall in the gastric potential but did not produce an acid secretion. A good correlation was observed between the secretory rate and the potential difference following ethanol-saline on histamine activated mucosae. Rice & Ross (24) have reviewed the literature relating to the electrical potential of the gastric mucosa and have described an amplifier operating a high resistance galvanometer. Potential changes and secretion were recorded photographically. Initial experiments on man displayed an almost continuous fluctuation of voltage closely aligned with emotional factors. In dogs under urethane, urethane and chloralose or barbiturate anaesthesia, the recording electrode was inserted through a gastrostomy with the esophagus and pylorus tied off. The resting voltage ranged between forty and one hundred millivolts, the mucosal surface being negative to the serosal surface. Local trauma or painful stimuli of other parts of the body decreased the potential difference across the mucosa. Pilocarpine and histamine reduced the gastric potential, the reduction persisting approximately throughout the duration of their therapeutic effectiveness. Fundic potential was higher than the pyloric potential. No significant change occurred when 25 cc. of 5 per cent sucrose were introduced into the stomach. At death, produced by an air embolus or intravenous chloroform, an initial precipitous drop was replaced by a gradual flattening of the potential which terminated in the mucosal surface becoming positive with respect to the serosal surface.

Lutwak-Mann & Barrett (25) found that in whole segments of rat cardiac gastric mucosa, under anaerobic conditions, only the mucosa disintegrated. The addition of 0.0025*M* glucose or mannose prevented autolysis. Fructose, galactose, glycogen, and hexosephosphates were poorly glycolised. Respiration was only slightly affected by prior anaerobiosis. Under aerobic conditions the gastric mucosa maintained its enzymic activity and structure.

The rate of aerobic glycolysis was not more than about half that due to lactic acid formed from glucose anaerobically. Although sulphonamide strongly inhibits carbonic anhydrase it does not inhibit gastric hydrochloric acid secretion even when present in the gastric mucosa in sufficient concentration to inhibit more than 99 per cent of the enzyme, yet thiocyanate ions, though less markedly inhibitory to carbonic anhydrase inhibit acid secretion. Davenport (26) has therefore stated that the term "Carbonic Anhydrase Theory of Gastric Acid Secretion" is a misnomer.

When increasing amounts of glucose, 25 to 75 gm., were incorporated in a farina test meal administered to eighteen young males, van Liere *et al.* (27) found that the higher the concentration of glucose the longer the emptying time of the stomach. When a charcoal-acacia mixture was given by a stomach tube to anaesthetised dogs with an average blood sugar of 99 mg. per cent, the average distance traversed in the small intestine was 183 cm. (range, 128 to 300); after the blood sugar had been raised to an average of 285 mg. per cent by intravenous glucose injection the average distance was 141 cm. (range, 83 to 258). In young female rats gastric emptying time and intestinal absorption were greater with large volumes than small volumes of equal concentration and with concentrated solutions when contrasted with dilute solutions of equal volume (28). Similar results were obtained when cereal starch was fed to rats (29). Adult rats fed 1.4 gm. corn oil, on exposure to 53 mm. Hg pressure of oxygen, showed an initial acceleration of gastric emptying time with a decreased rate of absorption of fat (30). Harris, Grossman & Ivy (31) have demonstrated in the dog that the motor inhibitory factors in urogastrone and enterogastrone are active only in the vagally innervated stomach. Ten milligrams of urethane of β-methyl choline, thirty to sixty minutes before a meal, have been used to restore gastric motility after a transthoracic bilateral vagotomy; one subject required the drug for eighty-five days postoperatively (32).

Peptic activity has been determined in highly diluted gastric juice by estimating the amount of egg, bovine, or human serum albumin digested; the undigested albumin is precipitated with sulphosalicylic acid and its density measured photoelectrically. The quantity of albumin digested is proportional to the logarithm of the pepsin concentration (33).

Harper (34) has made an alcoholic extract of hog pyloric and intestinal mucosa which can cause the secretion of hydrochloric acid in the chloralosed cat and is without depressor action. It was not dialysable and was inactivated by peptic digestion. Gastrin has been biologically assayed in urethane-chloralosed cats; one secretory unit is equivalent to the amount of gastrin producing 1 ml. 0.1*N* hydrochloric acid per hour. A good proportionality was obtained unless the test dose produced more than 10 to 12 ml. 0.1*N* hydrochloric acid per hour (35).

Intravenous benadryl (β-dimethylaminoethylbenzhydryl ether hydrochloride) at a dosage of 10 mg. per kg. body weight inhibited gastric motility but increased the rate of secretion in chloralosed cats infused intravenously with two to seven μg. histamine per kg. per min. (36). In man the same drug, given parenterally in maximum nontoxic dosage before the intravenous infusion of 0.01 mg. histamine base per minute, caused some inhibition of volume and acidity of histamine-induced gastric juice (37). Sulphonamide administered in ten gram doses to five normal men produced an increased secretion and a hyperacidity of the gastric juice; a gastritis was also incurred (38). Babkin & Karp (39) found that 0.2 to 0.3 gm. quinine bisulphate or 0.05 to 0.1 gm. atabrin intravenously in dogs weighing 8 to 15 kg. caused a marked decrease in volume and pepsin content of the gastric secretion produced by rhythmic vagal stimulation. Quinine and possibly atabrin had the same effect when given intraduodenally; quinine *per os* slightly inhibited the vagal secretion; the inhibition increased after withdrawal of the drug. Atabrin had a more definite inhibitory effect in a dog with an esophagotomy and a gastric fistula. Pilocarpine hydrochloride subcutaneously at a dosage of 0.4 mg. per kg. body weight did not stimulate the secretion of mucus in an everted pyloric pouch in the dog. Following the injection the mucosa changed from a bright red to a purplish red colour; no movements of the pouch were observed (40).

The mucin content of gastric juice has been determined by the turbidity produced by alcohol precipitation of mucin after prior precipitation of protein with picric acid. The mucin content ranged from 0.15 to 1.5 per cent in 313 specimens obtained from fifty healthy and ninety subjects with various gastric disorders. No definite relationship between macroscopic mucinity and

mucin content was observed. After a test meal the mucin content was slightly higher than in the fasting juice; neither histamine nor insulin affected mucin content. No clear differences were observed in the mucin content of the gastric juice of normal subjects or patients with peptic ulcer or gastritis (41).

Apperley (42) has compared the effects of a gruel meal with the ingestion of 250 cc. of 0.4 per cent hydrochloric acid in man. Gastric acidity and emptying times were determined by the neutralizing and diluting powers of the duodenal fluids which in turn were dependent on the secretory activity of the various glands which secreted into the duodenum and on the chemical composition of the blood. Ingestion of ammonium chloride or inhalation of carbon dioxide slowed gastric evacuation, whereas sodium acetate accelerated it.

Isocaloric replacement of part of the oatmeal of a basic test meal with sucrose, lactalbumin, butter fat, or hydrogenated vegetable oil exerted no significant effect on gastric motility (43). Gastric hypermotility induced by burns in the dog, under pentobarbital, was completely inhibited by doses of atropine up to 80 mg. but the drug had no effect on the increased gastric secretion (43a).

The gastric response to a toast and water meal has been examined in forty-seven normal subjects over sixty-five years of age. True achlorhydria occurred in eight subjects but proteolytic activity was absent in only one of these. A hyperchlorhydria was present in 12.7 per cent (44). No relationship between gastric acidity and thiamine excretion in the aged was observed (45).

Wolman (46) has examined the gastric phase of milk digestion in fifty-nine children aged three to fourteen years. Wide variations in volume and acidities were met in the fasting juice. Cow's milk was coagulated in an average of 19.7 min. (range 8 to 52); the mean emptying time was 118.5 min. (range 25 to 170). Apart from coagulation little proteolysis occurred in the stomach. Price (47) has exposed omentum, intestine, liver, gall bladder, spleen, kidney, lung, cartilage, skin, and stomach wall to gastric digestion in healthy dogs. The living tissues were implanted in the lumen of the stomach or in a gastric window. Virtually all tissues were digested even in the presence of an intact blood supply. The external coats of hollow organs were digested the most rapidly; fibrous connective tissue, skin, and intestinal mucosa were more

resistant but only gastric epithelium remained immune from gastric digestion. Contact surfaces were digested less readily than those which projected into the lumen. The cellular reactions to digestion in living tissues differed markedly with the tissue concerned; serous surfaces became acutely inflamed with rapid leucocytic infiltration and necrosis; omentum and the capsules of the spleen, liver, and kidney showed an excessive fibrosis; muscle produced a granulation tissue at the corroding surface which acted as a barrier to further action of the acid chyme. Once the tissues were covered with a proliferating gastric epithelium further digestion by the normal gastric juice was inhibited.

Wolf & Wolff (48) found that the gastric mucosa is more easily damaged mechanically when it is engorged. Under normal conditions it is very resistant to noxious stimuli; ipecacuanha and mustard caused no visible change in the gastric mucosa which is protected by mucus. Large gastric rugae simulating a tumour (49) or forming a transpyloric prolapse (50) have been reported.

A study of the gastric sediment of normal and pathological subjects has been made by Tomenius (51).

Peptic Ulcer

In the rat ulceration of the antrum or the fundus has been induced by tying the single antral artery or one or both vessels supplying the fundus (52) or by a low calcium diet in very young rats or by starvation in older rats (53). Ulceration produced by pyloric ligation and starvation was prevented by transabdominal vagotomy (54) and also by a mixture of sodium dodecylsulphate and colloidal aluminium hydroxide which reduced acidity and peptic "activity" (55). Jensen (56) reported that 67 per cent of rats receiving not more than 0.57 μg. vitamin A daily developed severe gastric lesions in the fore stomach and especially at the junction of the cardiac and pyloric regions; as little as 0.5 mg. daily of α-tocopherol afforded complete protection. Peptic ulceration occurred in dogs subjected to experimental burns unless the haemoconcentration was combatted (57). Ascorbic acid aided the healing of, or afforded some protection against, cinchophen experimental peptic ulcer in the dog (58) but benadryl failed to prevent histamine induced ulcer in the guinea pig (59).

Bonney & Pickering (60) have shown in man that the naturally reoccurring pain in peptic ulcer is relieved by emptying

the stomach and can be reinduced by returning the gastric contents but not if these are first neutralized or replaced by an equal volume of isomolar sodium chloride solution. Pain in peptic ulceration is caused by a certain degree of acidity acting for a certain time on a defective gastric or intestinal mucosa and is not due to a general or localized contraction of the stomach or duodenum. Infiltration of 2 per cent procaine round the intercostal nerves in the anterior axillary line from the fifth to eleventh thoracic segments on one or both sides abolished the pain set up by the intragastric injection of 0.1N hydrochloric acid and the tenderness exhibited on deep palpation. They concluded that the time relations of pain in peptic ulceration are compatible with the chemical stimulation of pain nerve endings situated in the ulcer crater and separated from the cavity of the stomach by a layer of functionally inert material.

Smith, Ruffin & Bayliss (61) reported that the instillation of 300 cc. of 0.5 per cent hydrochloric acid into the stomach of a patient with peptic ulcer produced pain which abated suddenly when the anaesthesia reached the sixth thoracic segment, if a spinal anaesthetic was administered. A negative response to acid was obtained after transthoracic vagus resection, although the sensations of distension, traction, hot, and cold were still present.

The occurrence of a gastroduodenitis which may or may not be associated with a gastric ulcer is reported in twenty-seven members of a family in three successive generations. It is regarded as a simple dominant hereditary disposition (62). Of 3,684 patients who sought medical attention for gastrointestinal disturbances, 168 showed serious teeth defects which had been present for at least eighteen months, making proper mastication impossible. Whereas only 6.1 per cent of the 3,516 patients with a more or less efficient mastication had a primary gastritis, the incidence in the toothless patients was 48.8 per cent (63). Kiefer & McKell (64) have reported 152 cases of peptic ulcer in patients over sixty-five years; in half of these the onset of ulcer symptoms occurred after their sixtieth birthday. In general their symptoms were atypical, pyloric obstruction was relatively frequent when the ulcer was situated in the duodenum, and gross haemorrhage with tendency to recurrence was noted in a third of their subjects. Doyle (65) has revived the view that gastritis is caused by an allergy to common foods; the gastritis results in a hypersecretion which

produces ulceration in an area of diminished resistance. The importance of the emotions in the production of gastrointestinal disturbances (66) and peptic ulcer (67) has been emphasized.

From an examination of a hundred consecutive "tests of healing" of gastric ulcers from the case records of the University of Michigan Hospital it was found that of the sixteen outpatients whose first follow up x-ray was made between twenty to sixty-three days after beginning treatment, five healed within thirty-five days, the earliest in twenty-seven days, one was not healed in 111 days. Of the in-patients thirty-three remained under treatment until a negative x-ray was obtained; average healing time was twenty-five days with a range of ten to fifty; thirty-eight benign ulcers failed to heal during hospital treatment lasting eight to forty days (average, twenty-three days). No significant effect of sex, age, duration of symptoms, recurrences, type of treatment, associated duodenal ulceration, or maximum acidity after histamine was observed (68).

Smith (69) has compared the effect of nonreactive aluminium hydroxide and amphogel in the treatment of hospitalized peptic ulcer patients; no differences in the results were observed. The action of anion exchange resins has been studied in rats by Segal *et al.* (70). In male rats a slight loss in weight, with some mucosal and submucosal changes, was observed when formaldehyde resin formed 20 per cent of the diet. No loss in weight occurred in the female rats and the red and white cell counts, haemoglobin, and blood chlorides remained normal. Kraemer & Lehman (71) administered three to five grams of resin four or eight times a day to eighteen proven peptic ulcer patients; they observed no advantage over treatment with salts of aluminium, calcium, or magnesium. When resin was administered to normal adults after an Ewald test meal, Spears & Pfeiffer (72) found that although 0.25 gm. resin reduced the acidity, not until 6.4 gm. were given in at least two consecutive half-hour doses did the free acidity fall to zero for at least one hour. Out of thirty patients with peptic ulcers, most of whom had a long history of ulcer pain, twenty-nine experienced relief of pain within five minutes, even subjects with marginal ulcers, but this ensured no guarantee of healing or recurrence or complications, nor did the amount of resin required bear any relationship to the relief of the pain. The resin also relieved the pain, at least in part, in twenty-three other patients with ab-

dominal pain other than peptic ulcer pain. Hodges (73) and Kemble (74) have utilized protein hydrolysates in the treatment of peptic ulcer in man. The former used a mixture of amigen and dextrimaltose in two-hourly feeds, giving the equivalent of 285 gm. protein a day. Most of his patients experienced complete relief in forty-four days; twelve out of twenty-three had no x-ray evidence of ulcer in two to three weeks, but three showed no evidence of improvement. The latter treated fifteen peptic ulcer patients, mostly duodenal, with 1500 cc. of a 6 per cent protein hydrolysate daily, for an average of nine days by gastric drip or intravenously. In nine out of thirteen patients the ulcer disappeared as judged by x-ray examination.

An antiulcer factor, which has been assayed against experimental ulcer induced in the rat by ligature of the pylorus, has been isolated from human urine (75). After clarification, the factor is absorbed on norite, eluted with 60 per cent acetone in water at pH 2.0 and precipitated with 90 per cent acetone. A yield of 3.25 gm. was obtained from a hundred litres of urine. Intravenous doses of fifty to one hundred milligrams protected the rat against ulceration if administered at the time of tying the pylorus. Hubacher (76) has reported on the effect of a protein and lipoid-free extract (Robudan), prepared from the stomach or upper part of the small intestine, on 54 subjects with peptic ulceration. A water-soluble part is given intramuscularly, the insoluble fraction *per os*. The progress in thirty-three subjects was followed by x-ray examination: indurated ulcers responded poorly; improvement rarely occurred before the tenth injection or before fourteen days on tablets only; three relapses occurred in sixteen months. The preparation of an enterogastrone concentrate and the results obtained after parental administration to experimental and clinical peptic ulcers have been reported by Ivy and his colleagues (77). The final product was dissolved in boiling water and in sterilized containers kept its potency for ten days. Therapeutic trials on forty-three Mann-Williamson dogs and fifty-eight proven peptic ulcer patients, who were given three or six injections of two hundred milligrams per week, showed that the concentrate was effective in preventing recurrences during the period of administration and for an undetermined time afterwards. The results cannot be ascribed to a true inhibitory action of enterogastrone.

The effects of a transthoracic vagotomy upon the clinical course of thirty patients with peptic ulcer have been reviewed by Ruffin, Grimson & Smith (78). Half of their subjects had previously had one or more operations before the vagotomy. The follow-up averaged nine months but ranged from twenty days to twenty-one months. Since vagotomy, all had been free from ulcer pain; appetite, hunger pains, and satiety were normal. Although fourteen patients had previously had gastric haemorrhages none were encountered postoperatively. Epigastric fullness was always associated with gastric retention; it frequently followed vagotomy, persisting for three to four weeks. Abdominal pain due to extragastric causes was unaffected. The volume of gastric juice in the fasting stomach was half that prior to the operation, and up to four months postoperatively contained no free hydrochloric acid. Free acid gradually returned but was never so high as before the operation, whilst in general values for combined hydrochloric acid increased. Vagotomy produced a marked delay in emptying with moderate dilatation and a diminished or absent peristalsis. Twenty patients retained a barium meal for more than six hours; three required surgical treatment for gastric retention. Moore and his colleagues (79) have reviewed the effects of resection of the vagus nerves for peptic ulcer in thirty-seven patients. In thirty-two subjects the ulcers were healed with only three unsatisfactory results. Of the twenty-nine satisfactory results five had transient gastrointestinal symptoms—diarrhoea which ceased spontaneously, postprandial epigastric fulness; one patient had to revert to antacids for "ulcer pain." Their findings are comparable with those just quoted. In addition, they noted the chloride ion secretion mirrored that of the hydrogen ion, pepsin concentration was variable, and motility returned to a nearly normal level in three months. The threshold of pain to balloon distension in the esophagus, stomach, duodenum and small intestine was unchanged by vagus resection.

The gastric mucosa has been observed through a gastrostomy by Wolf & Andrus (80) before and after a bilateral vagotomy. The response to tactile, temperature, and pressure stimuli remained the same, but after vagotomy no spontaneous motor activity was observed and only a mild hyperaemia of the mucosa after a meal. After the exhibition of prostigmine bromide the rugae reddened and a mild degree of motor activity was displayed.

Hollander (81) has described a test which has been widely employed to detect the presence of intact nerve fibres after vagotomy or vagus resection. The test is performed ten to fourteen days postoperatively and is repeated at intervals. On the day before the test, the subject is placed on a Sippy diet but no food is given after 19:00 hours and no fluid after midnight. Next morning the fasting stomach contents are withdrawn and the stomach tube left *in situ*. A fasting blood sugar is obtained and then fifteen units of insulin are given intravenously; the stomach is emptied every 15 min. for two hours and a blood sugar specimen taken after every second aspiration. If the blood sugar falls below 50 mg. per cent in the presence of some vagal nerve fibres, the normal stomach exhibits a biphasic response—first an alkaline followed by an acid secretion; when the vagal fibres are completely divided, only the alkaline response is obtained. A monophasic response does not prove that all fibres have been cut, a definite hypoglycemia of at least 50 mg. per cent, a pre-existent anacidity, or neutralization by regurgitation must be carefully checked.

Bradley & Small (82) and Miller & Davis (83) have reported that in more than 90 per cent of cases a transabdominal subdiaphragmatic surgical approach will allow as nearly a complete division of all the gastric nerves as will a transthoracic approach. Grossman, Cummins & Ivy (84) have compared the effect of 0.25 to 0.5 units of insulin per kg. body weight subcutaneously on the food intake of a normal and vagotomised-sympathectomised dog. Insulin produced an identical augmentation of food intake in both groups of animals. It is suggested that insulin hypoglycaemia acts directly on the brain to excite food intake activity. Froehlich (85) has reported on twenty-five cases of peptic ulcer treated by splanchnectomy and ablation of the first lumbar ganglion; nine results were good; five who had previously had a partial gastrectomy gave a bad end result; some abdominal pain persisted even when the ulcer healed in five cases; whilst in three cases a small ulcer crater persisted. Pereira (86) found that single or repeated anaesthetic block of the splanchnic nerves and the first lumbar ganglion gave encouraging results in the treatment of peptic ulcer, cardiospasm, and visceral pain, and had a favorable result on the healing rate of gastric ulcer in dogs.

Adlersberg & Hammerschlag (87) have studied a group of

fourteen patients who were unable to gain weight over a number of years following a partial gastrectomy for peptic ulcer. Early postprandial symptoms were occasioned principally by mechanical factors: small stomach, rapid emptying, overloading of the small intestine; late symptoms were biochemical, a postprandial hypoglycaemia occasionally secondary to a disturbed intestinal absorption. The loss of weight, hypoproteinaemia and vitamin deficiencies encountered in relatively mild intestinal lesions have been ascribed by Standard (88) to the hypermotility induced by an inflammatory lesion such as gastrojejunocolic fistula, ulcerative colitis, or tubercular ileitis which allows practically no time for absorption. Nutritional deficiencies may themselves cause hyperperistalsis. Rehydration, remineralization, protein replacement, and finally surgical removal of the organic aetiological agent were advocated.

A case of Hodgkin's disease in which the condition originated in the stomach and in which x-ray examination suggested ulcer and gastritis has been described (89).

Since 1915, twenty-three cases of gastroileostomy have been reported. Three additional cases have been described by Brown *et al.* (90). The predominant symptoms were loss of weight and pain relieved by vomiting; the vomit may contain faecal matter. Renshaw *et al.* (91) established four gastrocolic, one anterior and one posterior gastrojejunocolic, and one duodenocolic anastomoses in dogs. The major part of a barium meal entered the upper part of the small intestine. All dogs lost weight, had a steatorrhoea and a hypochromic anaemia after two to six months. Colonic material regurgitated into the stomach. At necropsy the stomata were four to six centimeters in diameter, the gastric mucosa was normal or showed a catarrhal inflammation, whilst a diffuse patchy hyperaemia with an inflammatory infiltration of the mucosa was present in the duodenum and upper jejunum.

Pancreas

Elman & Schwarz (92) have reviewed the recent literature. Doubilet (93) has described an ingenious physiological procedure by which the presence of an accessory pancreatic duct can be visualized. The normal resistance of the sphincter of Oddi can be raised from 150 mm. water to 300 mm. by one-sixth grain morphia subcutaneously, to fall to 200 mm. in one hour; or to 250 mm. water for ten minutes following intraduodenally administered

0.1*N* hydrochloric acid. If the sphincter is moderately spastic, iodized oil can be made to ascend the main pancreatic duct to pass out through the accessory duct. Montgomery, Entenman & Chaikoff (94) found that pancreatic juice *per os* prevented the development of fatty livers in the completely depancreatized insulin controlled dog. Thomas & Crider (95) using dogs with gastric and duodenal fistulae obtained, after intravenous insulin to produce a blood sugar of 30 to 40 mg. per cent, a rise in the specific gravity of the pancreatic juice with increased enzymic content but no increase in volume. Herfoot (96) has reported a case of hyperinsulinism in which an adenoma was successfully removed; a comparison of aspirated secretin-stimulated duodenal contents before and after operation showed that during the hyperinsulinism the pancreatic lipase and trypsin were diminished. The threshold dose of a standard preparation of secretin plus pancreozymin showed a tenfold increase in alloxan-diabetic dogs but remained practically at normal values in the alloxan treated nondiabetic dog (97). In chronic fistula dogs Thomas & Crider (98) found that atropine or hyoscyamine, in doses sufficient to block secretory endings of the vagus, decreased the specific gravity and total nitrogen content of the juice regardless of the stimulus used to promote secretion; peptone, alone, given into the intact gut produced an increase in the volume secreted under these drugs. A case of pancreatic lithiasis caused by actinomycete is reported by Dalgaard (99). Rienhoff & Baker (100) have described a case of chronic pancreatitis and pancreolithiasis in which relief of pain was only obtained following a bilateral transthoracic vagectomy and a bilateral sympathectomy from the fifth thoracic to the second lumbar ganglia with coeliac ganglionectomy. Waugh & Clagett (101) have reported on thirty cases in which resection of the duodenum and head of the pancreas was performed for carcinoma with a mortality of 20 per cent. A postcolic antiperistaltic gastrojejunostomy made distal to a pancreaticojejunostomy and a choledochojejunostomy gave best results. Lipp (102) has reported in one case of acute pancreatitis a decreased serum calcium which returned to normal values as the serum amylase declined.

Small Intestine

A preparation of the circular components of the muscularis mucosa of the small intestine of the dog has been described by

King, Glass & Townsend (103). It was shown to have an adrenergic and a cholinergic innervation. Whereas the longitudinal component of the muscularis mucosa had the same relative contractile power in any part of the small intestine, the maximal contractions of the circular fibres were greatest in the ileum where spontaneous and induced contractions were most pronounced. Contractions of the small intestine induced by splanchnic stimulation and by epinephrine are mediated through the muscularis mucosae. Visceromotor reflexes, most easily elicited in the decerebrate preparation with the cord cut between thoracic segments two and six have been described by Downman & McSwiney (104). Visceromotor reflexes underwent extinction before the viscerovascular reflexes. Mesenteric or pancreatic stimulation was more potent than intestinal stimulation. Gernandt & Zotterman (105) have examined the afferent impulses from abdominal viscera transmitted in splanchnic and mesenteric nerves of the cat. No flow of impulses was observed when the gut was touched; pinching produced spike potentials belonging to the slow δ fibres. Intense stimulation gave rise to large potential waves apparently built up by slow C potentials. An apparatus by which drugs can be applied to the serosa or mucosa of the isolated intestine has been devised by Meyer & McEwen (106). Choline esters introduced into the intestinal lumen of ileal loops prepared from guinea pigs or rabbits under pentobarbital anaesthesia tended to stimulate first peristalsis then pendular movements; atropine applied to the mucosa decreased peristalsis but exerted less effect on the pendular movements. Choline esters applied to the serosa stimulated both movements but spastic tonus of the longitudinal muscles interfered with both, especially the pendular movements. When atropine was applied to the serosa after either atropine or choline esters had been introduced into the lumen tonus was abolished but peristalsis might persist. Their findings suggest that, if autonomic drugs are effective orally, they do not act locally on the gut but are first absorbed into the circulation. Dibutylurethane of dimethylethyl β-hydroxyethylammonium sulphate administered in 5 to 10 mg. doses intramuscularly every four hours relieved the pain of chronic nonspecific ulcerative colitis, and colonic and functional pylorospasm (107). By direct microscopic observation Abell & Page (108) showed that intravenous angiotonin and renin caused constriction of the arteries of the mesen-

tery and intestine in the unanaesthetized rabbit; the capillaries were unaffected. Both substances promoted a vigorous intestinal peristalsis. The effect of anaesthetics on the propulsive motility of the small intestine of the dog has been studied by means of charcoal-gum acacia suspension fed by a stomach tube or after injection into the duodenum of the anaesthetized animal. The progress was greater after gastric intubation but many animals failed to empty in the five minutes which elapsed between the gastric intubation and the initiation of the anaesthesia (109). Necheles, Walker & Olson (110) have recorded the gastrointestinal motility in unanaesthetized dogs with chronic fistulae and in acute experiments under deep ether, evipan, or morphine anaesthesia before and after small, moderate, or massive haemorrhage. The motility of the colon was almost uniformly increased to at least 50 per cent above the basal level; that of the stomach, antrum, and duodenum varied with anaesthetic employed but was usually depressed. Gregory (111) observed the motility and tone of double Thiry Vella loops in the upper jejunum of a dog following minimal subcutaneous doses of apomorphine to cause four bouts of emesis in thirty minutes. The first signs of nausea were accompanied by inhibition of motility and tone lasting thirty seconds followed by an abrupt increase in both. Retching movements ended in a single powerful effort of emesis, during which the viscera were compressed. Between and after emesis the intestinal tone and motility resumed their normal appearance. Denervation of one mesenteric pedicle abolished the response in that loop. Wolf (112) carried out fluoroscopic examinations of the stomach and duodenum of a young soldier in whom nausea was induced by discussion of jungle fighting. Gastric relaxation with inhibition of peristalsis preceded nausea by as long as one minute and outlasted the vomiting by three to fifteen minutes. Duodenal contractions showed a reduced frequency, and an increased amplitude and duration.

Simple intestinal obstruction has been produced in the dog by dividing the intestine and inverting both ends with a single silk suture (113). The division was made twenty centimeters below the pylorus or at midileum or at the terminal ileum. Water *ad libitum* up to one litre per day but no electrolytes was allowed. Dogs with high obstruction showed no damage to the intestinal wall and the average survival time was nine days (range, 5 to 14);

and midileal dogs survived an average of 5.5 days (range, 3 to 8); low ileal dogs 7.7 days (range, 2 to 26). The majority of animals in the last two groups showed some damage to the intestinal wall and, although there were no gross perforations, distension occurred sooner and to a greater extent and was accompanied by kinking. The pancreatic activity of the intestinal contents showed a remarkable decline in potency from jejunum to ileum. At necropsy the pancreas was found to have undergone an average atrophy of 66 per cent in high obstruction and 50 per cent in middle and low obstruction. Biggs & Pontius (114) have reported five cases of intestinal obstruction of the newborn. In two of these where 111 and 55 cm. of the ileum were resected the subjects developed a coeliac-like syndrome. One thousand newborn males were examined radiographically between the fourth and seventh day of life; in none was any abnormality of the pyloric canal observed. Five developed a pyloric stenosis after three weeks; roentgenographic pathognomic signs appeared within two weeks (115). An ileoileal intussusception resulting from the intubation of the small intestine has been reported (116). Seven cases of a volvulus of the small intestine apparently caused by sudden over loading of a loop or loops by inbibition of more than a litre of maize meal gruel were reported by Kerr & Kirkaldy-Willis (117) in adult East African natives. The contents were evacuated through a low enterostomy before the distended bowel was reduced. According to Ogilvie (118) the East African is immune from peptic ulceration; the stomach is larger and the small intestine several feet longer than those of a European with a longer and more extensible mesentery. The successful recovery following an extensive resection of small and large intestine following an acute superior mesenteric artery thrombosis is described by Meyer (119). All the gut from the upper twenty inches of the jejunum to the midcolon was excised and a lateral jejunocolostomy performed in a nineteen year old private. Six months later he was passing two soft stools on a high carbohydrate, low fat, and moderate protein diet and gaining weight. Haemoglobin and red cell count were practically normal.

Aetiology of ileus has been designated by Chesterman (120) as a neuromuscular imbalance. Under certain conditions a flattening or even a reversal of gradients in the intestinal tract is produced. He found that in the dog under chloroform ether

anaesthesia a spinal anaesthetic relieved the neurogenic ileus produced by iodine irritation of the bowel and that the injection of 70 per cent alcohol between the leaves of the mesentery in man caused the vigorous contractions of the gut to be replaced by distension after two minutes with a decrease in movement below the distension. The wall of the distended loop could be stimulated directly. Devine (121) has reviewed the literature of paralytic ileus; overdistension of the stomach caused loss of tone and decreased motility of the small bowel; barbiturates decreased peristalsis and tonus; a physiological ileus followed each abdominal operation. He has divided ileus into three phases: (*a*) movements are active and co-ordinated, responsive to stimulation, and effective; (*b*) movements are irregular, un-co-ordinated, and ineffective; and (*c*) disappearance of intestinal movements.

Intestinal absorption.—Gregory (122) has applied the technique of London cannulae to sheep and goats. Administered as a 10 per cent solution, galactose was absorbed from the upper human intestine at an average rate of 11.2 gm. per sq. m. of body surface per 30 min. (123). Sherlock & Walshe (124) have used a portal anastomatic vein for studies of the absorption of galactose, glucose, fructose, and fat. Vitamin B-deficient rats exhibited a decreased intestinal absorption of glucose; when the whole vitamin-B complex was restored to the diet glucose absorption was supranormal during recovery (125). Staehelin (126) found that a vitamin B-free diet did not alter the ratio of the absorption of xylose and glucose in the isolated gut of the rat; nor did adrenalectomy in the normal animal, but adrenalectomy in the B-deficient animals markedly depressed the absorption of glucose.

Fat absorption and digestion have been reviewed (127). Basu & Nath (128) found that mustard, cocoanut, sesame, and ground nut oils were completely utilized by man; hydrogenation appeared to affect their digestibility. Artom & Cornatzer (129) considered that the supply of choline or its precursors might be a limiting factor in phospholipid synthesis during fat absorption in the rat. Finely emulsified paraffin was not absorbed from the rat's intestine (130). Smart & Daley (131) have examined the aspirated contents of the small intestine in ten subjects with sprue and in eight normals, before and after a meal of 25 ml. of olive oil. Fat appeared in thirty to ninety minutes; in sprue white threads and clumps in a relatively clear bile stained fluid

were found. The more severe the sprue the more marked the clumping of the mucin. Van Zeben (132) found that carotene is absorbed to the extent of 25 to 45 per cent from raw spinach or raw grated carrot but the absorption from the cooked material or preserved tomato juice was considerably less. No correlation between carotene and the vitamin A-content of blood serum was observed. Sodium phytate decreased the calcium and increased the phosphorus absorption in infants (133) and in children (134). Granick (135) has shown that feeding ferrous iron to the guinea pig led to the formation of ferritin in the mucosal cells of the small intestine and so regulated iron absorption. The relative permeability of the small intestine of the dog to magnesium and sulphate ions was not altered by anaemic anoxia (136). Govan & Darrow (137) obtained excellent results when they employed 70 to 150 cc. per kg. per day of an infusion fluid containing 33 m*M* potassium, 122 m*M* sodium, 104 m*M* chloride and 53 m*M* lactate per litre to replace the fluid lost in diarrhoea in infants. The rate of inflow never exceeded two cc. per minute and was only employed when the kidney was secreting urine.

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BLOOD CYTOLOGY[1]

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Since Radiant Energy, Shock, Blood Clotting, and Hemostatics and Anticoagulants are covered in other chapters in this volume, they will not be included in this chapter. Even with these exclusions and merely citing the reference and giving the subject matter of reviews and monographs related to blood cytology, a complete bibliography would require more space than the allotted fifteen pages, so of necessity many important articles must be omitted. Some articles have been selected because of their great interest and others because they require critical comment, which accounts for the fact that some of the articles included are less important than some not included. Greatest attention will be paid to folic acid, nitrogen mustards, urethane and stilbamidine.

New Developments in General Hematology

The most important developments have been the appearance of a new journal and the formation of two new societies. The first issue of *Blood*, (The Journal of Hematology) appeared in January, 1946, and issues have appeared bimonthly since that date. With an able editorial board, headed by William Dameshek, the bimonthly issues have maintained a high standard of original articles and include, also, editorials, news and views, abstracts, and book reviews. The publishers, Grune and Stratton, are to be congratulated on a pleasing format and typography.

Two new societies are in the process of formation. One is an informal Hematology Club to meet before the annual meeting of the American Society of Clinical Investigation in Atlantic City so that internists interested in clinical hematology may discuss together problems of mutual interest. The other is an International Society of Hematology which will meet biannually probably in two cities

[1] This review covers the period from July 1, 1945 to July 1, 1947.

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in adjacent countries and will provide an opportunity for presentation of more formal papers and closer association between hematologists of all countries. Information about the Hematology Club may be obtained from Dr. William Dameshek of Boston, Mass., and about the International Hematology Society from Dr. Joseph Hill of Dallas, Texas.

A number of new texts or new editions of texts or atlases of hematology have appeared, but space does not permit their inclusion.

Reviews and Monographs

Minot & Castle (1) have reviewed the literature on diseases of the blood and blood-forming organs. Reinhard *et al.* (2) have reviewed the literature on radioactive phosphorus as a therapeutic agent and presented much original data on the treatment of leukemias and polycythemia with this agent. Furth (3) has reviewed recent experimental studies in leukemia. Cartwright (4) has written an excellent review with a bibliography of 665 titles on dietary factors concerned in erythropoiesis. Thannhauser & Schmidt (5) have reviewed the lipidoses and the chemistry of the lipins found in the reticuloendothelial system in these conditions. McCutcheon (6) has reviewed chemotaxis in leukocytes.

Aleksandrowicz (7) has written a monograph from Poland on the technic of biopsies of the marrow, spleen and lymph nodes. Fieschi & Astaldi (8) have written a monograph in Italian on in vitro culture of bone marrow with over three hundred references to the Italian, English, German, French and Russian literature. Bover (9) has written a monograph on diagnosis by sternal puncture in Spanish with many illustrations and over five hundred references. Paseyro (10) has written a monograph on the diagnostic value of preparations made from material aspirated by puncture of the lymph nodes, spleen, liver or bone marrow, based on several hundred cases he has personally studied. Hemmeler (11) has written a monograph on infectious anemia in French published in Switzerland which emphasizes that the anemia of infection is normocytic, associated with a low plasma iron, and results from decreased formation of erythrocytes in marrow and, therefore, is not benefited by iron therapy.

The Erythrocyte Series

Hemoglobin and hemoglobin derivatives.—Watson (12) in a very important paper has outlined and reviewed his evidence for the

newer concepts of the natural derivatives of hemoglobin. Protoporphyrin, not hematoporphyrin, is the porphyrin from which heme is formed by addition of one atom of ferrous iron for each molecule of protoporphyrin. The reticulum stained with brilliant cresyl-blue is free protoporphyrin uncombined with protein, but protoporphyrin may be combined with protein or heavy metals and, therefore, be present in increased amounts even when the reticulocyte count is not elevated. There are four heme molecules attached to one globin molecule in hemoglobin, since the globin molecule alone has a molecular weight of 60,000 to 70,000.

In the normal transition from hemoglobin to bile pigment, the first change is the splitting of the alpha-methene bridge to form verdohemoglobin, which is the green pigment (biliverdin-iron-globin). Loss of the iron with addition of two atoms of hydrogen produces bilirubinglobin, a substance responsible for the indirect or total minus one minute-reacting serum bilirubin. In passage through the liver cell the globin is split off to form the sodium bilirubinate of the bile which, if reabsorbed or regurgitated into the blood stream, gives the direct or one minute serum bilirubin and is excretable by the kidney, but has a variable renal threshhold. Bilirubinglobin is not excreted by the kidney.

There are really two urobilinogens in feces and urine, mesobilirubinogen and stercobilinogen, formed by reducing bacterial action in the colon in that order. The two corresponding oxidation products, urobilin 9, α and stercobilin, are collectively designated urobilin. For clinical purposes, the terms urobilinogen and urobilin are satisfactory to designate the sums of the two pairs of compounds, since the urobilins can both be transformed to the urobilinogens and urobilinogens give equal quantitative response in the Ehrlich reaction.

While bilirubin can be formed from hematin, it cannot be formed from protoporphyrin, and hematin occurring naturally in the blood in hemolytic anemias is always bound to the albumin fraction corresponding to Fairley's methemalbumin. When iron is split off from verdohemoglobin or the hematin of blood, it combines with globulin to form the serum iron, whereas the hematin and verdohemoglobin and bilirubin migrate with the albumin fraction.

Normal range of concentration of erythrocyte protoporphyrin is fifteen to forty micrograms per 100 cc. of erythrocytes, usually less than thirty micrograms. Values are increased in all patients with reticulocytosis, in iron deficiency anemias, heavy metal poi-

soning, myelophthisic and hypoplastic anemias, with the highest values, fifty to six hundred micrograms, in heavy metal poisoning and iron deficiency anemias.

Shemin & Rittenberg (13), using N^{15} labelled glycine, which is incorporated in the protoporphyrin of heme and not re-utilized, computed the life span of human erythrocytes to be 127 days, confirming previous studies by the Ashby technic made by many authors. This technic of using N^{15} labelled glycine for studies of hemoglobin formation and destruction offers great promise of providing much information on the rate of red cell destruction and the fate of the pyrrol ring of hemoglobin in various diseases and will probably be used widely in the future by those equipped for such studies. This study clearly indicates that the duration of life of the normal erythrocyte is a function of its age and not random destruction.

De Vries (14) concludes from studies made on ten patients afflicted with malaria that the quantitative summation of total urobilinogen output in the stools and urine is the only unequivocal evidence of increased blood destruction as the values of hemoglobin, red cell count, reticulocyte count, icterus index, quantitative van den Bergh, and urobilinogen in urine may be normal in the presence of active blood destruction.

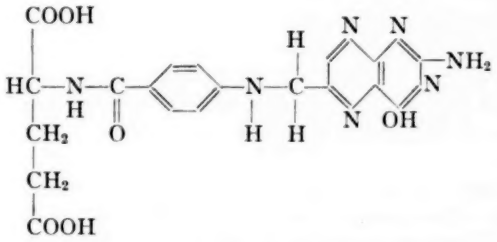
Erythropoiesis.—Krogh (15) has reviewed the important studies of Plum and co-workers on the production and ripening of red blood cells. These Danish workers have demonstrated in plasma and liver extract a reticulocyte ripening principle. The potency of the plasma factor is greatly increased by addition of traces of tyrosine. The pyloric mucosa of pigs contains the highest concentration of this ripening factor, suggesting a possible relationship to the intrinsic factor of Castle. These workers also investigated the mechanism of the formation of red blood corpuscles and concluded from quantitative studies in embryos and in modified Osgood marrow culture apparatus that mitotic division could not account for the erythrocyte production. Even when mitotic activity was stopped by colchicine erythrocyte production continued, and in a small chamber in which erythropoiesis could be observed directly under the microscope, erythrocyte production by pinching off of the cytoplasm of nucleated erythrocytes could be observed directly.

Hamre (16) has studied hematopoiesis in the bone marrow of rats recovering from nutritional anemia induced by an exclusive

milk diet following administration of iron and copper. He believes that erythropoiesis, as well as the development of other cells of the marrow, is exclusively extravascular.

Schwarz (17) found from studies of blood and marrow in normal and diseased conditions that giant cells of the erythrocyte or granulocyte series may be the result of division of the nucleus without corresponding division of cytoplasm. The greatest number of nuclei found in one cell in the erythrocyte series was eight.

Folic acid.—In a series of articles published in monographic form in the Annals of the New York Academy of Sciences, the story of folic acid is summarized by the men who have had most to do with it (18). This article, the reviews by Berry & Spies (19), and Thomson (20), and the monograph by Spies (21) should be consulted for references, since so many have appeared related to this subject that space will not permit their inclusion in this review. The isolation, identification and synthesis of pteroylglutamic acid, now usually called folic acid, and related compounds have clarified much previous work in nutrition and raised many new problems for investigation. The full chemical name of pteroylglutamic acid and its structural formula is given below:



N—[4-{[(2-amino-4-hydroxy-6-pteridyl)methyl]amino}benzoyl]
Glutamic acid

It is probably identical with vitamin M, factor U, factors R and S, vitamin B_c, and the norite eluate factor or *Lactobacillus casei* factor from liver, and folic acid from spinach. Synthetic folic acid differs from vitamin B_c conjugate, fermentation *Lactobacillus casei* factor, factor SLR, and the norite eluate factor from yeast only in having but one glutamic acid radical, whereas the other compounds have three to thirteen such radicals and can be broken down to

folic acid by an enzyme called vitamin B_c conjugase. Pteroylglutamic acid is chemically related to several substances previously shown to be necessary for the nutrition of at least some species, including xanthopterin and *p*-aminobenzoic acid, and folic acid effects have been demonstrated in at least some species by thymine and alpha and beta pyracin in addition to all of the above-listed substances.

Characteristic folic acid effects are the stimulation of growth of *Lactobacillus casei* and a strain of *Streptococcus fecalis* known as *Streptococcus lactis R*, and correction of a nutritional macrocytic anemia, leukopenia and thrombocytopenia in many species, including man.

In doses of 10 to 50 mg. daily orally or even smaller amounts intramuscularly, it has been abundantly proved to correct completely the anemia and leukopenia of tropical and nontropical sprue and nutritional macrocytic anemia, the macrocytic anemia of pregnancy, and, in the majority of instances, the blood and bone marrow pictures in pernicious anemia revert to normal with an adequate reticulocyte response. It has equally definitely been shown that it does not correct the neurological symptoms of pernicious anemia and that combined system disease and peripheral neuropathy may occur during the course of adequate or excessive folic acid therapy without any relapse in the blood picture. It is neither the extrinsic nor the intrinsic factor of Castle. It is not the substance present in potent liver extracts responsible for their action. It does correct the diarrhea and glossitis of pernicious anemia and sprue. A minimal maintenance dose in pernicious anemia has not yet been determined, but it is obviously not a satisfactory substitute for liver extract until a substance which will control the neurologic changes has been found to administer with it. It has been postulated, since enormous doses of thymine have a similar action, that liver extract may contain a factor which releases folic acid from the pteroylglutamic acid conjugates found in many foods and that folic acid is concerned in some way with the synthesis of thymine for nucleic acid formation.

Meyer (22) treated eleven patients with pernicious anemia and one with a sprue-like syndrome, following resection of the small and large bowel for regional ileitis, with folic acid. In six cases of pernicious anemia and one of the sprue-like syndrome treatment consisted of 15 to 50 mg. of folic acid orally or 20 mg. intra-

muscularly. In five cases of pernicious anemia, 5 to 10 mg, of folic acid with one-half unit of liver extract were given intramuscularly, daily. When no liver was used, there was usually a lower reticulocyte response than would be expected from adequate doses of liver extract. In three cases the plateau level of hemoglobin and red cell counts was below optimal normal. In three patients on folic acid alone, signs of combined system disease developed or progressed. The patient with the sprue-like syndrome showed a remarkable and complete hematologic recovery with great clinical improvement. Folic acid with one-half unit of liver extract daily produced in five cases of pernicious anemia a reticulocytosis greater than that anticipated with optimal liver extract alone and a complete hematologic remission.

Hall & Watkins (23) treated fourteen patients with pernicious anemia with pteroylglutamic acid (synthetic folic acid) over periods of twenty-four days to nine months. Some reticulocyte and erythrocyte regeneration responses were submaximal and peripheral neuropathy and subacute combined degeneration of the cord developed or progressed in some cases.

Spies *et al.* (24) treated three cases of pernicious anemia over a short period of time with 6 gm., and 10.2 gm. of thymine, respectively, in divided doses, daily and obtained slight rises in hemoglobin and reticulocyte counts which were certainly submaximal for optimal liver therapy, but were interpreted as comparable to those of folic acid. They speculate that thymine or a thymine-like compound may be synthesized from the action of folic acid as an enzyme or co-enzyme.

Miscellaneous observations.—Ross & Paegel (25) present a very thorough study of a case of acute hemolytic anemia due to sulfadiazine, during which a temporary spherocytosis and increased fragility of the erythrocytes developed in the absence of any hemagglutinins or hemolysins that could be demonstrated. The leukocyte count at its peak exceeded 63,000 per c.mm.

Massive doses of iron, 0.608 gm. to 1.32 gm., as colloidal ferric hydroxide or colloidal ferric oxide were administered intravenously to eight patients with hypochromic microcytic anemia by Goetsch, Moore & Minnich (26), who obtained reticulocyte responses higher than are usual after oral therapy. They plotted the rate of hemoglobin regeneration and conclude that the fastest rate of hemoglobin regeneration that can be stimulated by iron in hypochromic

anemia approximates 0.3 gm. per 100 cc. per day. Severe reactions occurred from this therapy and it is contraindicated except for research purposes.

Pace *et al.* (27) increased the hematocrit value of five normal young men from a mean of 46.2 to a mean of 58.3 per cent by transfusion of 2,000 cc. of a 50 per cent suspension of erythrocytes in glucose and saline solution with a resultant calculated increase in altitude tolerance from 10,300 feet to 15,500 feet.

Methods.—Blum (28, 29) has described a photoelectric method of erythrocyte counting. While a simpler and more accurate method of erythrocyte counting is urgently needed, examination of his data shows that he has proved conclusively in his own article that what is determined is hemoglobin and not erythrocyte count, and that close correlation between erythrocyte count and photoelectric colorimeter reading occurs only when the color index is normal. In the few macrocytic and hypochromic microcytic anemias reported, the photoelectrically determined erythrocyte counts all give color indexes within normal limits. Obviously, the only reason for doing an erythrocyte count is to get an accurate color and volume index, since the much simpler and more accurate hemoglobin determination would be sufficient if one could always assume the color index to be one. Any new method that purports to give erythrocyte counts, cell volume or hemoglobin must be tested on macrocytic and hypochromic microcytic anemias as others have made similar errors.

Meneely, Wells & Hahn (30) conclude from careful comparison of the Evans blue dye plasma volume technic of Gibson and the radioactive donor red cell technic of Hahn made simultaneously on the same subjects and in vitro that the dye method is unreliable. They conclude that the dye method is inaccurate because of a variable rate of removal of the dye by the reticuloendothelial system and its combination with albumin and that the total body hematocrit differs from venous hematocrits, the latter being constantly high. However, they presented no evidence that the cell volume determinations were made by centrifugation to constant volume rather than for a constant time at a constant speed. Centrifugation to constant volume is absolutely essential because of marked variations in sedimentation rates if hematocrit values are to be accurate. If in subsequent studies more attention is paid to centrifugation to constant volumes, which in bloods with different

sedimentation rates may take anywhere from twenty minutes to many hours at the usual *g* values used, this source of error, at least, could be eliminated.

The Leukocytic Series

Chemistry.—Wislocki & Dempsey (31) have studied the chemical cytology of normal blood and hematopoietic tissues of monkeys in a very important article which should be read in the original by anyone interested in histochemical technics. They investigated the content of iron, calcium, glycogen, nucleoproteins, and lipoids as well as of several enzymes and review such previous studies as are available in this field. Glycogen was found only in the neutrophiles. The basophilia of the cytoplasm of immature cells of the granulocyte and erythrocyte series is due to ribonucleoprotein. Lipoid material was demonstrated in blood platelets, megakaryocytic cytoplasm, and in neutrophile and eosiniphile granules.

Wagner (32) has made a well-controlled study of the glycogen content of leukocytes in leukemia and polycythemia, and he concludes that the reducing substances of lymphocytes and blast cells are not true glycogen but that true glycogen is found in the cells of the granulocyte series beyond the granulocyte stage in concentrations of 0.17 to 0.67 per cent of the wet weight. Values up to 1.64 per cent occur in polycythemia and up to 3.05 per cent in glycogen storage disease. His method of computing the glycogen content per million white blood cells and per microgram of wet weight should be of interest to anyone making studies of the chemical composition or enzyme systems in white blood corpuscles, more data on which are badly needed.

Wachstein (33) has reported his studies on the alkaline phosphatase activity of leukocytes in man as well as in laboratory animals. Phosphatase was found in neutrophiles and was increased by inflammatory stimuli and decreased in leukemia. Eosinophiles and lymphocytes were devoid of phosphatase activity.

Menkin (34) has continued his studies of extracts of inflammatory exudates. By incomplete hydrolysis of pyrexin, he was able to dissociate the leukopenic factor from the pyrogenic factor. He showed that necrosin did not reduce the number of leukocytes in dogs.

Hormonal effects.—Dougherty & White (35) summarize their important studies of alterations produced in lymphoid tissue by pi-

tuitary-adrenal cortical secretion and also the studies of others. Administration of pituitary adrenotropic hormone leads to a decrease in the total amount of lymphoid tissue and in the number of circulating lymphocytes with a concomitant rise in serum gamma globulin. These effects do not occur in adrenalectomized animals, nor does administration of the pituitary adrenotropic hormone prevent the hyperplasia of lymphoid tissue and increase in circulating lymphocytes which occur in untreated adrenalectomized animals maintained with desoxycorticosterone acetate. Desoxycorticosterone acetate has no significant effect on the lymphoid tissue of the intact or adrenalectomized animals. Corticosterone and Kendall's compound E do have effects similar to adrenotropic hormone in animals and man. A decrease in lymphoid tissue was associated with pyknosis and disintegration of some of the lymphocytes and a great loss of cytoplasm of other lymphocytes. A great variety of unrelated stresses produce similar effects to those of the adrenal cortical hormone. This antibody and gamma globulin release may play a part in the defense mechanism of the body mediated through the pituitary and adrenals.

Yoffey & Baxter (36) noted diminution of lymphoid tissue after four weeks' administration of pituitary adrenotropic hormone and an opposite effect or hyperplasia when extract of suprarenal cortex was administered to Wistar rats. When both substances were given simultaneously, the effect seemed to be neutralized. A lymphopenia occurred even though lymph nodes were hyperplastic when cortical extract was administered, without signs of degeneration in the nodes.

Nitrogen mustards.—Gilman & Philips (37) have reviewed the biological actions and chemistry of the nitrogen and sulfur mustards based on a large number of papers which are about to appear now that the war secrecy has been lifted. While a very large number of related nitrogen and sulfur mustards are possible and many have been studied, methyl-bis (β-chloroethyl) amine hydrochloride is the only one on which much clinical data are yet available. The action of all the compounds appears to be due to the release of a highly reactive onium cation on contact with water in slightly alkaline solution and not to the free chlorine as at first thought. This onium ion has a great affinity for many enzyme systems and exerts its greatest action on the nuclei and chromosomes of rapidly proliferating cells. While the actual duration of action is probably

less than a half hour before the active cation is completely gone, effects on mitosis and mutation persist over long periods of time and in *Drosophila* may even be inherited. In mammals the greatest effects are on the hematopoietic system and the gastrointestinal tract where proliferation of cells is most rapid.

Goodman and co-workers (38), as well as Jacobson *et al.* (39) and Rhoads (40), have presented the clinical results of their use of the nitrogen mustards in neoplastic diseases and other disorders. The therapeutic dose is close to the toxic dose and is generally given as 0.1 mg. per kilogram of body weight of the freshly dissolved drug rapidly given intravenously into a freely-flowing saline infusion daily or every other day for four doses. Toxic effects include extreme nausea, vomiting and diarrhea beginning in one to eight hours, usually three, and lasting for twenty-four hours, lymphopenia and granulocytopenia, thrombocytopenia and anemia developing in that order within twenty-four hours to four or five days and persisting for weeks and sometimes months. Although the effect on lymphocytes has been the most striking experimental result, clinical results in Hodgkin's disease have been much better than in lymphocytic leukemias or lymphosarcoma, and clinical results in granulocytic leukemias are comparable or better than those in lymphocytic leukemia. The clinical effects in Hodgkin's disease are similar to those of x-ray therapy, and somewhat similar results to those of x-ray therapy or radioactive phosphorus can be obtained in chronic leukemias or polycythemia rubra vera. The toxic effects, however, are much more severe than those ordinarily seen with skillfully applied x-ray therapy in Hodgkin's disease, and total body irradiation or radioactive phosphorus properly administered in the leukemias and polycythemia rarely give any untoward effects, so that from the standpoint of the welfare of the patient, it is probably better to defer use of these compounds except by qualified investigators until a well established method of treatment has failed to give further response. The compounds have also demonstrated some effectiveness in rapidly growing, anaplastic tumors, particularly bronchogenic carcinoma. Experimental studies of these drugs and related compounds should and undoubtedly will be continued because of the great theoretical interest of a known chemical compound which has effects so similar to those of ionizing radiation. It seems definitely possible, also, that smaller doses at regularly spaced intervals may prove less toxic and keep

the patient in a more uniform state of good health as the reviewer has shown is true with total body irradiation and radioactive phosphorus.

Urethane.—The observation by Haddow & Sexton (41) that urethane (ethylcarbamate) and related compounds led to a fall in leukocyte counts as well as regression of the Walker rat carcinoma 256, led Paterson *et al.* (42) to test the therapeutic effects of urethane on leukemia and carcinoma in human beings. The drug was administered in doses of 1 to 5 gm. daily, usually 1 gm. three times a day after meals. They administered it in a syrup, but it has been since shown to be equally satisfactory in capsules or tablets of 0.3 gm. size. Ten of nineteen patients with chronic granulocytic leukemia were considerably improved and five of thirteen cases with lymphocytic leukemia were also improved. In the eleven cases of lymphocytic leukemia in which urethane alone was used, the time taken for the count to fall to about 20,000 per c. mm. varied from nine to forty-seven days, averaging eighteen days. There was extreme variability in the susceptibility, doses required varying from 8 to 390 gm. Two cases were excluded, one aleukemic case in which the white count rose, and one case in which the white count had not reached this level in three months. In thirteen cases of granulocytic leukemia in which urethane alone was used, the amount of drug required varied from 19 gm. to 134 gm., and the time for a drop to 20,000 leukocytes per c. mm. varied between eleven and thirty-six days, the average being thirty days. In one case of lymphocytic leukemia, 390 gm. of drug were given in sixty-three days, with a still elevated leukocyte count. As a rule, the immature cells decreased more than the mature cells. The spleen and lymph nodes often regressed markedly in size. However, nausea and vomiting, leukopenia and drowsiness often made the clinical result unsatisfactory, although the white cell count was lowered. Temporary improvement occurred in three of the thirteen cases of advanced carcinoma of the breast treated, and, also, in four of eleven cases of other types of malignant disease. The action of urethane appears to be similar to that of a miscellaneous group of karyoklastic poisons. In marrow culture studies of urethane effects on human cells of the granulocytic series in the reviewer's laboratory with Dr. Chu-I-Tung (43, 44), the changes from control cultures noted were an initial stimulation of mitoses, the frequent occurrence of double nuclei and karyorrhexis and pyknosis of

nuclei. These effects were different from those of colchicine, nitrogen mustards or ionizing radiation. The nausea and vomiting and extreme variability in the response, sometimes giving rise to agranulocytosis, would suggest that irradiation or radioactive phosphorus administration will prove superior when an adequate time has elapsed for evaluation of this therapy. Urethane is certainly worth giving, however, in patients who have become resistant to ionizing radiation and in metastatic malignant tumors, although a response may be expected in only a small percentage of such cases, and in these it will be temporary.

Stilbamidine.—Snapper & Schneid (45) illustrate and describe deep blue staining inclusions in the cytoplasm of cells of the plasmacytic series when stained with Wright's stain which develop three to four weeks after therapy with stilbamidine has been started and doses totalling 1875 to 3600 mg. have been administered. In subsequent observations (46) presented at the meeting of the American Medical Association at Atlantic City in June, 1947, it was demonstrated that these inclusions consist of ribose nucleic acid in combination with stilbamidine instead of protein. The quartz microscope with the absorption band at 2,600 Å as a criterion for the ribose nucleic acid and the absorption band at 3,200 Å as a criterion for the location of the stilbamidine was utilized. They did not find similar inclusions in other bone marrow elements. This seems to be the most specific proof so far available for the mechanism of the direct localization of a drug in one area of one cell type and confirms the observations of Kopac (47) that stilbamidine will dissociate protamine from protamine ribonucleate in vitro. These stilbamidine granules stain a bright red with Unna's phenol methylgreen pyronine stain, while the azurophile granules occasionally appearing in myeloma cells do not stain with pyronine. This work suggests to the reviewer that if a radioactive element, ideally a short lived alpha emitter, could be incorporated in the molecule of stilbamidine or some related compound, truly specific localization might be obtainable for the treatment of myeloma and plasmacytic leukemia. Since the majority of plasma cells are located in the marrow, one might obtain more specific effects than from radioactive phosphorus in leukemias and polycythemias.

Snapper (48, 49) reports results of treatment of patients afflicted with multiple myeloma by stilbamidine (4, 4-diamidinostilbene) and pentamidine (4,4′-[pentamethylenedioxy] dibenzami-

dine) using fifteen or more intravenous injections of 150 mg. or 100 mg., respectively, given daily or every other day. The compounds produce, after five to six doses, stilbamidine granules in the myeloma cells and tend greatly to relieve the pain in the majority of patients without curing the disease or greatly affecting the x-ray picture. Toxic effects consist of a sharp drop in blood pressure, nausea and vomiting, and phlebothrombosis.

Leukemia.—Sacks & Seeman (50) have made an excellent statistical study of the mortality from leukemia between the years 1900 and 1944 and have noticed a continually increasing rate which is hard to account for by the age and sex distribution of the population, or even by improvements in diagnostic technics. Undoubtedly many deaths from leukemia are still not included in mortality statistics, but more than 5,000 persons died in the United States from leukemia each year since 1940. In 1942, more persons died in the United States from leukemia than from small pox, meningococcic meningitis, scarlet fever, poliomyelitis, malaria, typhoid fever and diphtheria combined. The mortality rate for white persons is more than twice that of nonwhites, and in males a third greater than for females. The highest rate, 15.7 per 100,000, occurred in the age group of seventy-five to eighty-four years. The lowest rate, 1.5 per 100,000, occurred in the ages from fifteen to twenty-four years. The death rate for the population under five years of age was higher than for any other age under forty-five years. The age-sex adjusted death rate per 100,000 population for leukemia in the United States death registration area increased from 1.4 per 100,000 in 1921 to 3.5 in 1940, and the crude death rate in 1940 was 3.7 per 100,000. Nine valuable tables of mortality statistics are presented, including one based on an analysis of 154 death certificates from Baltimore between the years 1939 and 1943 in which leukemia was classified as the cause of death in which the figures are classified as acute or chronic and as to the cell of origin. However, of these 154 records, only 87 per cent indicated the cell type and 63 per cent whether acute or chronic. The high incidence, 61 per cent, of acute leukemias in the Baltimore group may not give a true picture because of the fact that such patients are more often sent to consultation centers, but on the whole no more critical appraisal of leukemia death rates could be compiled than is given in this article until the diagnosis of the type and stage of leukemia is more accurately recorded on the death certificate.

Miller, Herbut & Jones (51) continue to study the myelokentric

acids and have treated eight cases of lymphoblastic leukemia with the crude substance. They present case histories and sections from these cases and from four controls in support of their view that the myelokentric acid is of value in the treatment of lymphocytic leukemia. Much more carefully controlled experiments with pure material would seem to be necessary before any conclusion could be drawn as to the value or even existence of these postulated interconvertible and antagonistic myelokentric and lymphokentric compounds.

Flory, Steinhardt & Furth (52) were able to prolong the lives of forty-six mice with chloroleukemia which had been injected twenty-four hours before with strain 1394 chloroleukemia cells. This strain was found more susceptible than other strains to 5 mg. of benzene given orally six times weekly. They emphasized that other types of granulocytic leukemia or lymphocytic leukemia were not as susceptible as this type. Sixteen of the forty-six mice failed to manifest the disease. The leukemic cells in the treated mice showed pyknosis of nuclei and karyorrhexis.

Kirschbaum & Mixer (53) studied the incidence of leukemia in eight inbred stocks of mice varying in susceptibility to spontaneous leukemia when these mice were divided into groups and treated with carcinogenic hydrocarbons, x-rays and estrogens, respectively. There was great variability in response to the different agents in the different strains of inbred mice. Only x-rays proved leukemogenic in nearly all strains. Only the carcinogen-treated groups showed a correlation between the induced and the spontaneous incidence of leukemia in the strain.

Miscellaneous observations.—Rebuck (54) has presented an extremely valuable summary of the literature and morphologic criteria for identification of the various types of giant cells found in the blood and blood-forming organs, illustrated with seventy-seven beautiful photomicrographs, including many from imprint preparations.

Sundberg (55) presents numerous excellent photomicrographs of material from imprints of human lymph nodes in a study of lymphocytogenesis. Many hematologists would disagree with her interpretation of her findings, and it seems doubtful whether this difference of opinion can be resolved until cultures started from a single clearly identified cell have been made or until some clear-cut histochemical criterion of cell identification is available.

Reinhardt (56) studied the growth of lymph nodes, thymus and

spleen and the output of thoracic duct lymphocytes in the normal rat from birth to nineteen months of age.

Bloom & Bloom (57) have studied the sequence of disappearance of cell types from the bone marrow following irradiation, usually with an LD50/30 day dose of x-rays, gamma rays, alpha rays, beta rays, and neutron rays. With all modalities and in all species they report decrease first in the erythropoietic cells, second in the myelocytopoietic cells, and third in the megalokaryocytes. Fat cells, free macrophages, and reticular cells seemed to be radioresistant to the dosage used. The modality of irradiation used made little or no difference except that with the alpha ray emitters only a narrow band of tissue was affected adjacent to the trabeculae in which the alpha ray emitter was deposited.

Kolouch, Good & Campbell (58) have presented evidence to indicate that plasma cells are concerned in the formation of globulin and that there is a hyperplasia of the plasmacyte series in hypersensitive states.

Tullis (59) has studied the resistance of the lymphocytes and neutrophiles of normal blood to isotonic and hypertonic and hypotonic media when these cells are incubated at 37° in vials in the marrow culture medium of Osgood and Brownlee and differed only in tonicity. They found that leukocytes could exist in tonicities varying between 220 and 380 milliosmoles (about 0.65 per cent to 1.25 per cent sodium chloride), that neutrophiles survive longest in isotonia and slight hypertonia (320 to 337 milliosmoles), and lymphocytes retain their morphological integrity longest in hypotonia. Eosinophiles were little affected by the anisotonia in the complete range studied from 237 to 380 milliosmoles.

Ayers & Geschicter (60) have made an interesting calculation of the duration of the intermitotic cycle in the granuloblasts and progranulocytes and of the life span of each cell of the granulocyte series from studies of sternal marrow in normal and leukemic individuals. While the method of calculation is probably sound, it is based on a number of assumptions that are open to question so that the absolute values are probably too high by a factor of at least two. He assumes a dilution of the marrow by a third with blood, a duration of mitosis of one hour, and that no cell death occurs except at the most mature stage. A similar type of calculation on marrow cultures in a state of equilibrium after determination of the duration from beginning cell disintegration

to complete autolysis, and an actual time-lapse determination of the duration of the process of mitosis for the particular cell type under those particular conditions might lead to more accurate figures.

The Thrombocyte Series

Aggeler, Howard & Lucia (61) have made a study of the platelet count, clot retraction, bleeding time, capillary fragility and coagulation time of sixty-four normal subjects and in four hundred and four patients with various diseases. They used the method of Rees and Ecker for platelet counting and found a normal range including plus or minus two standard deviations of 273,000 to 545,000 per c. mm. They emphasize, however, that normal values by other laboratories and by even different technicians in the same laboratory will show very significant variations, and they feel that for accurate interpretation, a normal value for each method and technician should be determined. They found a significant correlation of the platelet count with the clot retraction, the bleeding time and the capillary fragility test, but no significant correlation between the platelet count and the coagulation time. They rarely found bleeding in primary thrombocytopenic purpura unless the platelet count was below 190,000, nor in secondary thrombocytopenic purpura unless the platelet count was below 230,000 per c. mm. On the other hand, some patients with much lower platelet counts did not show an increased bleeding tendency. Since in all patients with active bleeding from primary thrombocytopenic purpura or secondary thrombocytopenic purpura the bleeding time was definitely prolonged and the clot retraction time diminished, these tests are much more reliable than the platelet count for diagnostic purposes in the majority of laboratories. The role of the platelets in the coagulation and clot retraction mechanism is well discussed, but the possibility that the low platelet count, prolonged bleeding time, delayed clot retraction, and capillary fragility may all result from a primary deficiency of thromboplastin is not mentioned. This concept seems to the reviewer more plausible than that deficiency of platelets is the primary cause of a deficiency of thromboplastin. This excellent paper is well worth reading in the original.

Lawrence & Valentine (62) found that they could significantly raise the level of the blood platelets in eight cats made thrombo-

penic by large doses of x-ray by carotid anastamosis with seven normal cats, and in one of the experiments with a splenectomized cat. Then after interrupting the cross-circulation, they plotted the rate of disappearance of the platelets from the blood of the irradiated cats and found an average rate of disappearance of 2,500 platelets per hour. They give reasons for preferring the term "rate of platelet utilization" to "life span." They believe that there is a complete turnover of platelets every three to four days in the cat.

Dameshek & Miller (63) describe a method of counting megalokaryocytes in sternal marrow and show photomicrographs and color illustrations of the various stages of development of the cells of the thrombocyte series. They give normal values for their technic and confirm the observations of previous investigators that these cells are increased in the marrow in idiopathic thrombocytopenic purpura. Their upper limit of normal is three hundred megalokaryocytes per million nucleated red cells.

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HEART[1]

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Anatomy

Davies & Francis (1) studied the conducting system of the vertebrate heart. In poikilothermic vertebrates cardiac muscle fibres form a continuum and have the same general histological characters in all parts of the heart. Cardiac contraction commences in the sinus musculature and is conducted throughout the heart by the muscle fibres. The delay in passage of the impulse from one chamber to the next is due to the arrangement of the muscle fibres rather than to any histological specialization at the junctional sites.

In homoiothermic vertebrates, however, specialized muscle has been evolved at certain places in the heart for the initiation and propagation of the impulse. This consists of nodal fibres with a high degree of intrinsic rhythmicity, and Purkinje fibres through which the impulse can travel faster than through the ordinary myocardium. These specializations may be correlated with the more rapid heart in homoiothermic vertebrates. The structure and distribution of these specialized fibres are for the main part similar in mammals and birds. The cardiac impulse is initiated in the sinoatrial node; it spreads thence throughout both atria, in mammals through the ordinary atrial muscle, in birds through the extensive network of atrial Purkinje fibres. The impulse then passes to the atrioventricular node and thence through the atrioventricular bundle which consists of Purkinje fibres but in some animals, such as man, the fibres closely resemble ventricular muscle fibres. The Purkinje fibres ramify beneath the endocardium but also throughout the myocardium of the ventricles, mainly periarterially. These fibres are directly continuous with the ventricular myocardium.

The principal differences between mammals and birds are (*a*)

[1] This review covers the period from July, 1945 to July, 1946.

the more extensive distribution of Purkinje fibres, including the atria, in birds, a feature which may be correlated with the more rapid heart rate in birds, (*b*) the presence of branches from the atrioventricular node to the muscular atrioventricular valve in birds, the valve contracting at the outset of ventricular systole.

Since there is no histological specialization of the muscle fibres in any part of the heart in poikilothermic vertebrates, factors other than purely morphological must account for the different intrinsic rhythmicities possessed by the individual chambers of such hearts. A differential distribution of certain chemical substances known to be concerned in muscular contraction is described which may have a bearing on this problem.

Harper (2) reports that the normal human and rabbit heart valves are largely nonvascular and contain no lymphatic vessels. In diseased valves blood vessels are formed as part of the inflammatory response. Particulate damage to the tricuspid valve of the rabbit by the intravenous injection of aleuronate induces a new formation of blood vessels in its cusps. A reticuloendothelial function can be ascribed to the subendothelial zone of the heart valve. He takes the view that organisms do not arrive in the valves through the blood stream, but are deposited on the surface. In rheumatic fever the reticuloendothelial function of the subendothelial zone of the valves may be stimulated and, if this stimulus is continued, these cells may be overwhelmed and vascularization of the valve cusps may follow. He draws attention to species differences in various mammals, some of which have vascular valves, and care must be exercised in the interpretation and comparison of the results of experiments aimed at the production of endocarditis.

Niehaus & Wright (3) are critical of loose statements concerning the apex beat. Inspection and palpation of the precordia of a thousand normal persons demonstrated the apex beat with certainty in only 24.6 per cent. They graded their subjects into those in whom there was no pulsation or some pulsation but insufficient to allow its use for estimation of heart size, on the one hand, and those in whom it was clearly palpable or visible, on the other. In young subjects it was clearly felt in 55 per cent, but as age advances it was palpable in only 10 to 25 per cent after the age of forty. The palpability of the apex diminished with increasing obesity.

Cardiac Output

The method of right heart catheterization introduced by Cournand & Ranges (4) continues to be widely used. Warren, Stead & Brannon (5) have published an analysis of the validity of the method. In thirty paired samples of arterial blood the variation never exceeded 0.4 vol. per cent difference between the first sample and the second. Drabkin *et al.* (6), using a continuous spectrophotometric method of recording, observed stability of the oxygen content of the arterial blood and therefore the differences noted in the arterial blood may be mainly technical. Differences of more than 0.4 vol. per cent must be taken as real. In 25 paired samples from the ventricle 17 showed a variation of less than 0.2 vol. per cent and 3 a variation between 0.2 and 0.4 vol. per cent. In 111 paired samples from the right atrium, 71 showed a variation of less than 0.2 vol. per cent, 17 differed by 0.2 to 0.4 vol. per cent, and 25 showed differences up to 2.3 vol. per cent. In 19 patients a comparison was made of atrial and ventricular samples. In 11 the variation was less than 0.4 vol. per cent, and in 6 between 0.4 and 1 vol. per cent. Some of these figures differed considerably from those found by Cournand (7), who reported that the differences. between atrial and ventricular samples taken simultaneously only exceeded 0.4 vol. per cent in three out of thirty-one instances. McMichael (8) points out that gross differences may be met with about once in twenty occasions. These reports emphasize the necessity for duplicate checking of right heart samples at critical points in all experimental observations. It is clear that in the majority of instances right atrial samples give a true picture of the composition of mixed venous blood. The meaning of occasional anomalous samples is not yet clear. They may mean a shift of the position of the catheter tip into a position where some incoming stream, such as the coronary sinus, is sampled, or they may indicate true fluctuations in the cardiac output. In this school we have noted them particularly when the right atrial pressure is undergoing some fluctuation. They are notably absent in heart failure where the possibility of cardiac output change is greatly reduced.

One of the defects of the Fick method is that it can only be an indication of the minute output when a steady state is reached, and changes in output from beat to beat cannot be followed. In order to get information on these points further studies have been

made on the use of a combined pulse pressure and pulse wave velocity measurement. The pulse pressure is theoretically dependent on the elasticity of the aorta and the volume of blood thrust into the aorta at each heart beat: the elasticity of the aorta is measurable from studies of the pulse wave velocity. Remington, Hamilton & Dow (9) review the difficulty in estimating the distensibility of the aorta from pulse wave velocity. Studies were made on dogs' aortas under various conditions. The aortic wall exhibits a complex tension length curve, due to the presence in its wall of three components, smooth muscle, elastic and collagenous tissues with different viscosities. Changes in tone of the muscle result in alterations in volume of the arterial tree and in the velocity of the pulse wave. Data obtained from these observations on pulse wave velocity and data of Wiggers & Katz (10) on volume pressure relationships were used to calculate the form of the ventricular ejection curve for dog and man: the curves obtained show fair agreement with cardiometer curves obtained experimentally [Remington & Hamilton (11)]. Hamilton, Dow & Remington (12) then analyzed the forces producing the human ballistocardiograph showing that this method of calculating cardiac output is a somewhat empirical procedure. The values obtained should be regarded as comparative rather than absolute. More extensive research is required to provide data for analysis of ballistocardiograms obtained under disease conditions.

The regulation of cardiac output.—The cardiac output in man was shown by McMichael & Sharpey-Schafer (13) to be regulated by at least three factors, the venous filling pressure (Starling's law), the heart rate, and epinephrine. Unstable and high outputs are particularly likely to be found in young subjects under emotional stress and in those who have a rapid heart rate. These complex factors probably account for some discrepancies between the work of the above writers and the data reported by Warren *et al.* (14). The question of whether the heart empties itself completely during systole is discussed by Nylin (15). With his radiological colleagues, he has found that the normal volume of the living heart is about 700 cc. The volume of the heart muscle is about 300 cc., which implies that the heart cavities contain about 400 cc. of blood. If the stroke volume of the heart is 140 cc. (70 cc. from each ventricle), then the residual blood in the heart at the end of systole will be 260 cc. The presence of such residual blood may explain the

changes which take place in the output of the heart under minute doses of epinephrine, which may produce a rise in output by as much as 50 per cent without any change in filling pressure, heart rate or arterial pressure [McMichael & Sharpey-Schafer (13)]. Nylin's studies emphasize another interesting point. Radiology of the heart at various intervals after death indicates that it undergoes some postmortem contraction which may interfere with the comparison of heart size after death with that calculated during life. In the large hearts of heart failure the residual blood may be very considerable (up to two litres).

The increased cardiac output of severe anaemia seems to be brought about by at least two factors, an increased venous filling pressure and a rapid heart rate [Sharpey-Schafer (16)]. Hunter (17) has shown that cardiac enlargement may be considerable in anaemia. Decrease in cardiac size tends to occur early in treatment. It does not follow the improvement in haemoglobin level, but may be dependent on a fall in the high venous pressure and cardiac output. As the blood volume in anaemia is low [McMichael *et al.* (18)], it is clear that there must be diminution of the capacity of the vascular bed. With a high cardiac output and a normal arterial pressure, the arterioles must be dilated and the reduction in the size of the vascular bed must take place on the capillary and venous side of the circulation. This is the type of evidence which is adduced to support the hypothesis of an active venomotor system in man. On the experimental side there is an abundance of evidence mainly from the school of Fleisch (19), that the veins are contractile and that they respond by contraction to such stimuli as acidosis and anoxia, thereby squeezing blood from the peripheral venous network towards the great central veins increasing the pressure at which blood is offered to the heart. Further evidence continues to accumulate on the contractility of veins. Silverskiold (20) has studied the effect of haemorrhage and shock on the caliber of the abdominal vena cava. Severe blood loss causes a great reduction of the width of the vena cava. In bled rabbits it may reach half its original diameter. The reduction in size was not passive, as it was uninfluenced by pressure on the liver, causing the pressure in the lower segment of the inferior vena cava to rise several centimeters. A similar reduction in size of the vena cava resulted when the blood pressure was lowered by squeezing the intestines. Ralston *et al.* (21) have repeated an old observation made by Riml (22)

who demonstrated that when the pulmonary artery of a rabbit is tied, and the cardiac drive to the circulation ceases, half the animal's blood may flow from the jugular vein. Henderson (23) recorded that the first gush of blood in similar experiments in cats would raise the pressure in the right atrium by 10 to 12 cm. Ralston and his colleagues found that the yield of blood flowing from the jugular vein was reduced from 40 ml. per kg. to 27 ml. per kg. by curare, suggesting that skeletal muscle tone was responsible for part of the blood flow. Clamping the splenic pedicle had little influence on the yield of blood.

Landis and co-workers (24) have made experimental studies of central venous pressure in relation to cardiac competence. In normal dogs, under anaesthesia, exercise of the legs produced by electrical stimulation lowers the venous pressure. Ligation of a coronary artery to produce a myocardial infarct does not raise the venous pressure, but exercise after coronary ligation will raise the pressure. Similarly, atrial fibrillation does not raise the venous pressure, but exercise in a fibrillating animal will produce a venous pressure rise. With pericardial tamponade the resting venous pressure was raised, but exercise lowered it as in the normal. With artificial hypervolemia produced by infusion of saline the pressure was temporarily raised, but exercise also lowered the pressure. They give a lengthy discussion of the significance of these data. It seems that the increased output of exercise in the healthy heart is effected by acceleration rather than by increased filling pressure, but in the presence of severe disturbance of function and cardiac damage an increased filling pressure occurs during exercise. Howarth, McMichael & Sharpey-Schafer (25) have reported on the effects of venesection in low output heart failure. In every instance they found that this method of lowering the filling pressure was accompanied by an increase in the cardiac output, sometimes to a considerable degree. They take this to indicate that the failing heart behaves like the overloaded heart of Starling's heart-lung preparation, in which a reduction in venous pressure may be accompanied by an increase in output. Further support is given to this hypothesis by Sharpey-Schafer's report (16) on the effects of blood transfusion in severe anaemias where the increased filling pressure may be accompanied by a fall in heart output.

The influence of respiration on the circulation.—Lauson, Bloomfield & Cournand (26) have studied the respiratory changes in

optically recorded pressure curves from the right atrium and right ventricle in man. The amplitude of the atrial waves increases during inspiration when the minimum intrapleural pressure falls to −7 mm. Hg. The effective filling pressure of the heart, or net pressure, is equal to the hydrostatic filling pressure plus the negative intrathoracic pressure. The net pressure is about 12 mm. Hg in inspiration and about 4 mm. Hg during expiration. The greater filling pressure during inspiration leads to a greater ventricular pulse pressure, probably indicating a greater systolic output. At the beginning of inspiration, however, the femoral arterial pressure falls slightly due to the exertion of a negative intrathoracic pressure on the aorta. Although the output of the right heart is increased at the beginning of inspiration, the increased output is accommodated in the pulmonary vessels and the filling of the left ventricle may be reduced. A little later the left ventricle gets the increased flow and the systemic arterial pulse pressure and systolic pressure both rise. When a Valsalva experiment is done, the rise in intrathoracic pressure is immediately accompanied by a decrease in the amplitude of the right ventricular pressure pulse. After a lag of two or three beats, the femoral pulse pressure also decreases and the systolic pressure falls. A Mueller experiment, on the contrary, leads to an increased output from the right ventricle. Cough produces an abrupt rise in intrathoracic pressure with a rise in arterial pressure. A single cough does not transmit a raised pressure back outside the thoracic cage to the peripheral veins as the intrathoracic veins accommodate all the blood dammed back. In cardiac congestion, however, a single cough may raise the peripheral venous pressure. Abdominal breathing may raise the filling pressure of the right heart by squeezing blood from the abdomen during inspiration, and may thus diminish the fall in hydrostatic pressure which occurs during ordinary thoracic inspiration. There is a very close correlation between the "net pressure" and the systolic pressure in the right ventricle. Systolic pressure and pulse pressure in the right ventricle are also closely correlated. Starr & Friedland (27) have studied the respiratory changes in circulation by means of optical arterial pressure records and ballistocardiograms. The latter tracings show changes which reflect alterations in cardiac output and are not due to change in position of the heart resulting from the rise and fall of the diaphragm. In sinus arrhythmia slowing of the heart was accompanied by small ballistocardiographic

variations, i.e. reduction of stroke output. This reduction in rate and diminution of cardiac impacts normally occurred during expiration, but could become inspiratory in time when inspiration was accompanied by a positive pressure blast, equal to 20 cm. water, through an inhalation mask; this procedure reversed the normal negative intrathoracic pressure in inspiration. In a normal subject, deep inspiration diminishes the arterial blood pressure by as much as 15 mm. Hg. During obstructed breathing through a narrow tube, the arterial pressure falls during inspiration, while the ballistocardiogram increases in amplitude. These data support the interpretations of Lauson *et al.* described above. During inspiration the filling and output of the right heart are increased, but the expanding lungs at first accommodate this increased inflow and it is only after an interval of several seconds that an increase in output of the left heart takes place. The slowing of sinus arrhythmia occurs during that part of the respiratory cycle in which the cardiac output is smallest, no matter whether this occurs during inspiration (as in the positive pressure experiments above described) or expiration. The arrhythmia is therefore due to changes in cardiac filling rather than to alterations in position or stretch of the lungs. This supports the well known view that sinus arrhythmia results from changes in cardiac filling induced by respiratory movements. It appears as though the heart waits to be filled during the slow phases.

Otis *et al.* (28), using a ballistocardiograph, have shown that breathing against an increased pulmonary pressure decreases the stroke volume and increases the heart rate. Breathing against a pulmonary pressure which is only raised during inspiration decreases the stroke volume and also the pulse rate so that cardiac output is also decreased to about 85 per cent of normal. Breathing pure oxygen decreases the cardiac output by 8.5 per cent. Whitehorn, Edelmann & Hitchcock (29) found that the cardiac output decreased by 13 per cent after five minutes and 19.4 per cent after sixty minutes of oxygen breathing. The heart rate slows and part of the decrease in output is accounted for by this. The early bradycardia of oxygen breathing in animals has been found to be of vagal origin, probably activated by some chemoreceptor mechanism. Otis and his colleagues noted that lowering of the alveolar carbon dioxide tension decreased stroke volume and increased the heart rate; the latter was not sufficient to compensate and the cardiac

output was estimated to fall by 5 per cent. Kety & Schmidt (30), however, found that cardiac output was reduced by 11 per cent during passive hyperventilation, but was kept normal during active hyperventilation by the accompanying tachycardia.

Right heart pressure in man.—Optical records of right heart pressure have been made by Bloomfield *et al.* (31). The general form of the curves is familiar from animal work. They found that in the supine position the distance from the sternal angle to the midpoint between the anterior tip of the ventricle and the lowermost part of the atrium was $5.8 \pm .9$ cm. In cardiac enlargement it was 5.5 ± 1.5 cm. and in emphysema $6.86 \pm .80$ cm. Five centimeters below the sternal angle was therefore taken as zero for the measurement of both atrial and ventricular pressures. Events in the atrial cycle are (*a*) a rise of pressure due to atrial systole; (*b*) a sharp rise of pressure due to closure of the tricuspid valves; (*c*) a fall in pressure due to descent of the base associated with ventricular ejection; and (*d*) a fall of pressure associated with opening of the tricuspid valve and the onset of ventricular filling. In the right ventricle the maximum systolic pressure varies from 18 to 30 mm. Hg with an average of 25 mm. Hg. The pressure in diastole varies from -7 to $+2$ mm. Hg at the lowest level reached after closure of the pulmonary valve (Pd_1) while the pressure at the end of atrial systole just before ventricular contraction (Pd_2) varies from -0.5 to $+4.5$ mm. Hg. The variations in pressure in various pathological states are fully analysed. The systolic pressure in the right ventricle is, of course, the same as the systolic pressure in the pulmonary artery. In emphysema without associated heart failure five out of nineteen cases had normal right heart pressures, while the others showed pulmonary systolic pressures ranging from 34.5 to 57.5 mm. Hg, the right ventricular pulse pressures in the latter instances being also high (30 to 54 mm. Hg). The onset of heart failure in emphysema produced a rise of pulmonary systolic pressure to 68 mm. Hg in one case. In mitral valve disease with heart failure the pulmonary arterial pressure reached as high as 103 mm. Hg, falling to 57 mm. Hg with recovery from failure. Essential hypertension without heart failure was associated with normal pulmonary arterial pressure. The onset of heart failure is associated with a whole series of changes in the form of the right heart pressure waves for which the original paper should be consulted.

Pericardial tamponade.—Fletcher (32) reported a case in which malignant disease of the mediastinal glands involving the base of the pericardium produced a serosanguineous effusion. The cardiac output was 4 litres per minute and the right atrial pressure, though grossly raised, was about 8 cm. saline above the intrapericardial pressure. Tapping the pericardium lowered the pericardial pressure and right atrial pressure in parallel, but as the effective filling pressure (right atrial minus pericardial pressure) remained unchanged, the cardiac output was unaltered. At a later stage the cardiac output is, of course, decreased, and a number of such cases have been studied by Warren *et al.* (33). Lyons & Burwell (34) have made a report on constrictive pericarditis: the stroke output tends to be fixed by the rigid casing round the heart and fluctuations in venous pressure are without effect on cardiac output; changes in output are dependent on rate only. Atropine produced an increase in cardiac output and a fall in venous pressure.

Effects of centrifugation.—Franks, Kerr & Rose (35) made studies on the circulation during acceleration designed to throw the blood from the head to the feet. There was an increase in heart rate with shortening of the P-R interval in the electrocardiogram. The size of the heart decreased, the face became blanched, and it was apparent that the return to the heart fell off and blood pressure was reduced. Experiments done on cats by Greenfield (36) showed that immersion in water up to the cardiac apex raised the acceleration necessary to bring the carotid pressure to zero from 4 g to 10 g. Subendocardial haemorrhages were sometimes found after excessive spinning.

Some general circulatory reactions.—Bradley *et al.* (37) report that the induction of a pyrogenic reaction, the fever being prevented by premedication with amidopyrine, increased cardiac output with an increase both in pulse rate and stroke volume, while simultaneously the peripheral resistance fell. In normal subjects the blood pressure was maintained at adequate levels, but in two hypertensives it fell considerably. In those hypertensives in whom blood pressure was maintained a considerable fall was produced by standing up, when a fall in cardiac output was responsible. Renal vasodilatation occurred during these reactions. Weens & Heyman (38) noted cardiac enlargement in patients treated with intravenous typhoid vaccine: this enlargement might persist for as long as

six months. It is difficult to account for this persistent enlargement on the basis of anaemia, cardiac overwork, etc.

Elkington, Danowski & Winkler (39) observed decrease in plasma volume in dogs with salt depletion and dehydration. Changes in venous return, cardiac output, and blood pressure were similar to those in traumatic shock.

Edholm, Howarth & McMichael (40) report an increased cardiac output (to over thirteen litres per minute) in a case of generalized Paget's disease of bone. This was accompanied by raised venous pressure and edema. Plethysmographic studies on the limbs of such patients established that there was an enormous increase in blood flow through the affected bones, which in the particular case described was calculated to have risen from a normal skeletal flow of approximately 100 cc. per minute to 3.3 litres per minute. Drury (41) reports the effects on heart size of experimental arteriovenous fistulae in rabbits. Radiologically the heart shadow is increased in size and the area of the shadow is clearly correlated with heart weight. After three months' patency the fistula was tied off. The hearts usually returned to their normal weight in eight weeks, the atria reaching normal values before the ventricles. Many of these hearts were up to twice the normal weight before closure of the anastomosis. In one animal, however, the hypertrophy did not regress. This observation may be very significant in that hypertrophy may become pathological and persistent after its cause has been removed.

Brannon, Weens & Warren (42) have studied the circulation in the presence of an atrial septal defect. The right atrial blood has a higher oxygen content than blood from the superior and inferior venae cavae, indicating the shunting of oxygenated blood from the left to the right heart. The output of the right heart may be twice that of the left heart.

Circulation Time

More methods continue to be recommended for the study of the circulation time. Wexler, Whittenberger & Himmelfarb (43) measure the circulation time from the lungs to the ear by causing the subject to take a single breath of nitrogen and measuring the time of arrival at the ear of unsaturated arterial blood, by means of an oximeter. In thirty-five subjects the range was 4.1 to 7 sec. The

value obtained avoids the variable arm-lung segment of the circulation. Gross (44) measures the lung-cheek circulation time with amyl nitrite. The time from inhalation to the appearance of a well-marked heat sensation in the cheeks is measured. The normal is 19.5 sec., the range 14 to 25 sec. The time is grossly prolonged in heart failure and figures like 31 to 54 sec. are then obtained. It is shortened in hyperthyroidism and normal in emphysema.

Nylin (45) thinks that the prolonged circulation time as measured by decholin may be taken up by mixing of decholin with a large amount of residual blood in the enlarged heart. He returns to this point in an article on the dilution curves of radioactivity in arterial blood after intravenous injection of corpuscles labelled with radioactive phosphorus. In normal subjects the radioactivity of the blood in the arm opposite to that in which the injection is made rises to a peak 15 to 20 sec. after injection. In the same subjects decholin times were also normal. Where the decholin time was definitely prolonged, for example to 37 sec., the concentration of radioactive corpuscles was already rising at the same time, but only reached its peak after 60 to 70 sec. Among his cases, however, was one of aortic regurgitation in which the decholin time was not prolonged in spite of the fact that the heart volume was estimated to be 1460 cc. It seems unlikely that with a cardiac output of at least three litres per minute in most cases of heart failure even a large amount of residual blood in the heart could lead to the great prolongations of circulation time observed.

Nylin's observations of the time-concentration curve, however, probably add point to the observations of Ruskin & Rockwell (46), who found that circulation times were related to dosage and volume of the test substance in such a way that low dosage or volume gave longer times.

Electrocardiography

Hecht (47) has carried out observations with a catheter-like electrode passed into the right heart, in order to prove some of the assumptions from animal work on which human electrocardiographic interpretation is based. When the electrode is inside the atrium near the sinus node, there is a large negative deflection which is taken to indicate that the electrode is situated close to a region of primary negativity. This region can never become positive in relation to the rest of the heart and hence a single negative

wave is characteristic of this situation. A little lower down in the atrium a small positive wave appeared and in a still lower part the positive wave became broader. Atrial extrasystoles showed either an increased or decreased positive (P_R) deflection when compared with the pattern of normal beats for that region. A sinus extrasystole recorded with the electrode placed at the sinus region showed a deep negative deflection (P_{QS}). From the inside of the atrium and from the ventricle, the ventricular deflections are characterised by deep negative (*Q-S*) deflections. The characteristic Q waves of myocardial infarctions denote the appearance of the potential variations of the ventricular cavities at the epicardial surface, these being transmitted through electrically inert infarcted and fibrosed areas. The human records presented are in accord with records of certain pertinent animal experiments, which have been based on the assumption that action currents may be represented as electrical doublets, or as an electrical source followed immediately by an electrical "sink," and that they follow the laws which govern flow of electrical currents in volume conductors. The matter, however, is by no means as simple as this, and it is difficult to reconcile the above conclusion with some other work. Nahum & Hoff (48) produced epicardial and endocardial extrasystoles by direct stimulation in animals. When the stimulating electrodes were immediately under the chest electrode, there was no difference between epicardial and endocardial extrasystoles. The initial wave of the complex was in every instance a simple downward deflection of *Q-S* type. Excitation of the area under the electrode is recorded by a downward movement in the electrocardiogram representing negativity at the chest electrode. This is the only process which can be responsible for the downward movement during the *QRS* component. Thorough exploration of all parts of the epicardium of the entire heart and all the endocardium of the right ventricle failed to reveal any other regions from which a *Q* wave could be elicited. These experiments, therefore, do not support Wilson's view (quoted by Nahum & Hoff) that the *Q* wave results when the subendocardial muscle of some part of the ventricular wall passes into a negative state earlier than the muscle which lies between the exploring electrode and the ventricular cavity. These results do not reveal the existence of currents associated with conduction of excitation from the endocardium to the epicardium.

Pruitt, Barnes & Essex (49) produced damage to the endocar-

dium and deeper layers of the myocardium in dogs. This led to diminution of the *R* wave or the development of a *Q*. Although there was extensive destruction of the tissues in which the Purkinje fibres are supposed to lie, the width of the *QRS* complex remained unchanged. The only lesion to lengthen the *QRS* complex was one high up in the septum. Bayley (50) reports a case in which there was more extensive myocardial necrosis on the endocardial surface then on the epicardial surface. A unipolar lead with exploring electrode over the injured region showed a downward displacement of the *RS-T* segment, opposite to that occurring in diffuse pericarditis. Clinicopathological correlations made by Pardee & Goldenberg (51) show that, unless the subepicardial layers are involved, the electrocardiogram rarely shows the typical curves of anterior or posterior infarction. The *Q* deflection in the precordial lead is associated with necrosis of the anterior part of the septum and may be present when this part of the septum is affected even without involvement of the anterior myocardial wall. Goldberger (52) discusses at considerable length the differentiation of normal from abnormal *Q* waves by unipolar limb leads.

The electrocardiogram in hypertension has been studied in considerable detail. Evans, Mathews & White (53) found that it was normal in 35 per cent, 27 per cent showed abnormal *T* waves, 16 per cent left axis deviation only, and 22 per cent showed a combination of left axis deviation plus abnormal *T* waves. Depression of the *R-ST* segment with lowering of the *T* wave in lead *I* was an early change. In the electrocardiogram in which *T* waves are normally inverted in lead III, inversion of *T* waves might appear first in leads II and III. The latter changes have not previously been emphasised and have frequently been misinterpreted as indicating coronary disease. Precordial leads may detect changes which do not show in limb leads alone. Canabal, Warneford-Thomson & White (54) show that these electrocardiographic changes usually progress and become worse. Over a period of 5 to 21 years, only 5 out of 50 patients showed spontaneous electrocardiographic improvement. White *et al.* (55) showed that lumbodorsal sympathectomy would lead to improvement of the electrocardiogram in most cases where these records were abnormal to start with. This improvement was associated with a return of the diastolic blood pressure to more normal levels. Goldberger (56) shows that similar improvement of the electrocardiogram may

follow inhalation of amyl nitrite. Inverted *T* waves may become upright, but if there is pronounced depression of the *S-T* segment, amyl nitrite may fail to produce much improvement. Stokes (57) indicates that amyl nitrite reversal of the inverted *T* wave in the electrocardiogram occurred in seven out of thirteen hypertensive cases. It also reversed the inverted *T* wave of myocardial infarction in six out of sixteen cases. In seven cases of aortic stenosis, amyl nitrite failed to produce any significant electrocardiographic change. This seems to indicate that the change is due to relief of the hypertensive load on the left ventricle.

Rhythm Disturbances

Levy *et al.* (58) report on the significance of transient tachycardia from a statistical analysis of the records of 22,741 Army officers. There is a significantly higher incidence of later hypertension and cardiovascular-renal disease in those with transient tachycardia, a finding similar to the significance of transient hypertension. The death rate in the group with transient tachycardia is less than in the group with transient hypertension. The coincidence of transient tachycardia and transient hypertension is twice as likely to lead to sustained hypertension as one of the two.

Holmes & Weill (59) report two healthy soldiers with prolonged *P-R* interval in the supine position which returned to normal on standing. Atropine produced the same effect. Manning & Stewart (60) reported similar cases.

Paroxysmal ventricular tachycardia in the absence of demonstrable heart disease is recorded by Lidman & Lyerly (61). The attack was accompanied by transient ventricular fibrillation and occurred in a subject aged twenty-one years. Normal rhythm was restored within one hundred sixty minutes by a total dose of 1.6 grams of quinidine by mouth. Eichert (62) also records bundle branch block in an otherwise normal heart above a critical rate of one hundred eighteen per minute. Master & Eichert (63) discuss cases of paroxysmal atrial fibrillation occurring without evidence of heart disease. The disorder occurred in naval personnel and was related to emotional and mental strain and perhaps excessive smoking and coffee drinking. Between attacks the rhythm was slow and ventricular extrasystoles were heard. Sensenbach & Buie (64) observed coupled beats in eight apparently healthy people who were not taking digitalis. The coupling lasted for short periods

and was associated with extrasystoles of the ordinary type. Here also emotional factors were considered important.

The Wolff-Parkinson-White syndrome of short *P-R* interval, prolonged *QRS*, with paroxysmal tachycardia, is the subject of numerous papers. Littmann & Tarnower (65) report nine cases and review the various theories. The most acceptable is that which assumes the presence of one or more accessory conduction pathways. Atropine produces shortening of the *QRS* complexes, which thus become more normal, while prostigmine widens the complexes. These substances, as well as quinidine and exercise, may be helpful diagnostic tests in border-line cases. Quinidine depresses the abnormal pathway, but Stein (66) reports that this effect is only recorded in two cases out of fourteen. Stein was also disappointed in the effects of atropine. The paroxysmal tachycardia occurring in this syndrome may be either atrial or ventricular, and sometimes atrial fibrillation occurs [Klainer & Joffe (67)].

Jones & Schlapp (68) induced atrial fibrillation in the cat heart-lung preparation by stimulating the atria fifty times per second. Fibrillation reduced the work capacity of the heart by approximately one third.

Coronary Circulation

Two excellent reviews have appeared by Gregg (69), and Ratnoff & Plotz (70). Gregg points out that some of the previous work has been modified by new anatomical and functional concepts. The right coronary supplies the right atrium and ventricle, while the left supplies the corresponding chambers. The sinoatrial and atrioventricular node are supplied by the right coronary, while the bundle branches are supplied by both coronary arteries. The veins are divided into deep and superficial. The deep or Thebesian veins open mostly into the right side of the heart, and the superficial veins which drain into the coronary sinus are mostly derived from the left heart. The anterior cardiac veins drain the right heart, especially in the dog. They lie in the sulcus between the right atrium and the right ventricle and empty into the right atrium just above the tricuspid valve. These two systems of veins communicate freely with one another.

Flow measurements are usually made in one coronary vessel only. This may or may not represent general directional changes in

total coronary flow. If arrangements are made to collect all the blood, the preparation becomes considerably removed from normal, which imposes a further limit on the interpretation of results. Various methods of recording blood flow in severed or intact coronary arteries are reviewed. The use of various preparations of the excised heart is criticised. Gregg thinks that more work should be done on the heart *in situ*. The curves of blood flow obtained under such conditions are grossly different from those in the excised heart.

Occlusion of the coronary arteries may be carried out, and, if the flow is gradually cut off, the whole of the main coronary supply may be interrupted with the development of collaterals from other cardiac and extracardiac sources. This may be achieved with minimal or even no infarction. When infarction does develop, the usual cause of death is ventricular fibrillation, which is thought to arise in anoxic areas of myocardium which become highly irritable. The mortality can be reduced by the development of collaterals by various surgical means. As a control on these measures for limiting the damage produced by coronary occlusion, no definite reduction of infarct size is seen after coronary venous occlusion, which of course prevents the effective development of any collateral arterial supply. Fauteux (71) reports that the mortality following ligation of the circumflex artery of dogs was reduced from 80 to 13 per cent by ligation of the great cardiac vein combined with pericoronary neurectomy. A human case of severe coronary disease and angina benefited considerably from this operation.

Anrep & Hausler (72), and Visscher (73) thought that when the load on the heart was increased by raising the pulmonary or aortic pressure the coronary blood flow was reduced by mechanical obstruction to the flow by a vigorously contracting heart. Gregg has used a more physiological preparation and found a greatly increased coronary flow under the same conditions. There is a very slight initial decrease in blood flow due to extravascular compression. This extravascular factor may, however, be more important when the preparation becomes more abnormal after a lengthy experiment. The left heart when overloaded is under a greater advantage than the right, as the increased aortic pressure automatically increases the pressure at which coronary blood is supplied.

Ratnoff & Plotz (70) quote from the literature consistent

figures of coronary blood flow from 60 to 176 cc. per 100 grams of heart per minute, depending on the circumstances under which the heart is working. Applying some of the physiological data to clinical problems they indicate that coronary blood flow is probably reduced during diastole in aortic incompetence, while in aortic stenosis the flow will be reduced in the early part of systole, and possibly also in the later isometric phase of ventricular contraction.

Katz, Wise & Jochim (74) emphasize that the coronary flow is determined by cardiac output and peripheral resistance. In experiments in which the heart rate was deliberately altered, the change in coronary flow was unpredictable. No effect of rate could be distinguished. Smith & Layton (75) studied flow through the left anterior atrial artery. A forward flow took place during both systole and diastole, but the flow was decreased by rise of pressure in the atruim. They suggest the possibility that such increased atrial pressures may account for atrial disturbances in the failing heart. Braun (76) reports that paravertebral blocking of the upper thoracic ganglia with novacaine produced improvement of the electrocardiogram in patients with angina pectoris. The *T* waves tended to return to normal. This improvement was not always accompanied by relief of pain.

Pharmacology and Metabolism

Acetylcholine.—Haney, Lindgren & Youmans (77) studied the acceleration of the heart which follows the bradycardia during the depression of blood pressure induced by acetylcholine. Sympathectomy reduces but does not abolish this response. It cannot be accounted for by reflexly liberated sympathin or reflex depression of cardioinhibitory tone. It seems necessary to postulate the occurrence of cardioaccelerator fibres in the vagus nerves, for, if both vagi are cut, the acceleration is almost completely abolished.

McDowall (78) reported a stimulating action of acetylcholine on the cat heart. Hoffman *et al.* (79) found that the injection of acetylcholine into isolated atropinized hearts of cats, dogs, rabbits, and guinea-pigs produces an epinephrine-like action, that is, an increase in heart rate and amplitude as well as a change of blood flow in the coronary vessels. The pharmacological characteristics of the stimulating action of acetylcholine on the heart are such as to designate it as a nicotine-like action. In the perfusate it is possible

to identify the presence of an epinephrine-like substance liberated when acetylcholine or nicotine is injected into the heart. Haney & Lindgren (80) noted that in dogs with denervated hearts (vagi and upper five to six sympathetic ganglia removed) the injection of acetylcholine accelerated the heart when the animal was atropinized. The acceleration might be as much as from 112 before injection to 350 per minute after injection. The action came on in four to seven seconds. The action is thought to be either a direct one on the heart or on intracardiac ganglion cells having an accelerator action. The latter explanation is the more acceptable.

Frohlicher (81) was able to stop fibrillation induced by electrical stimulation in perfused rabbit and dog hearts by the intracardiac injection of acetylcholine.

Digitalis.—Howarth, McMichael & Sharpey-Schafer (82) compared the action of intravenous digoxin with venesection. So far as the output of the heart is concerned, there is no statistical difference between the effects of mechanical reduction of venous pressure and similar reductions of venous pressure produced by digoxin. However, the blood pressure falls during venesection, whereas it is maintained after digoxin so that the heart does more work after the latter remedy. This leaves open the possibility in human heart failure of a direct stimulating action of digitalis on the myocardium. Ray & La Due (83) report on the intravenous administration of lanatoside C in half to full doses in patients who have developed heart failure while taking 0.1 to 0.3 grams of digitalis leaf daily. The dose of lanatoside C ranged from 0.8 to 1.6 mg. and sixty-two patients were thus treated. Before treatment twenty-four of these patients showed digitalis effects on the electrocardiogram. The therapeutic responses were very satisfactory except in one patient who gave deceptive information about his previous daily intake. He developed nausea and coupled beats, but these unpleasant reactions subsided after thirty-six hours. It is clear that electrocardiographic evidence of digitalis intake is not an index of a maximum therapeutic action.

Bond, Baum & Dimond (84) have used cerberin in patients with atrial fibrillation. This is a glycoside with a digitalis-like action. Given either intravenously or by mouth it controls ventricular rate more rapidly than digitalis, although its action was more transient. The clinical results also seemed satisfactory.

Quinidine.—Quinidine is considered by Askey (85) to be

worthy of trial in severely ill patients with marked congestive failure. The danger of death from the disease is greater than the danger of death from the drug.

Theophylline.—It is still claimed that theophylline is a coronary vasodilator. Mokotoff and co-workers (86) say that the size of infarcted areas following ligature of the left anterior descending coronary artery is smaller in dogs given aminophylline than in untreated dogs. Papaverine, however, is more effective. Smith & Jensen (87), using theophylline aminoisobutanol in the heart-lung preparation, showed that the drug produced striking stimulation of myocardial contraction with prompt restoration of strength of the failing heart after it had been poisoned with chloral hydrate. There was no evidence that this was the result of dilatation of the coronary arterial system. Steinberg & Jensen (88) used the same preparation on clinical cases. It caused a rapid fall in venous pressure which actually began during the injection, as well as a shortening of the circulation time. This action lasts for sixty to ninety minutes. The fall in venous pressure is not accompanied by any changes in plasma volume. In patients who were failing to react to other remedies there might also be no satisfacotry reaction to theophylline. They think that dilatation of small veins may be responsible for the venous pressure fall. Howarth, McMichael & Sharpey-Schafer (89) report somewhat similar actions of theophylline, emphasizing a venous pressure lowering action and a stimulating action on the heart.

Magnesium.—Szekely (90) reports that the intravenous injection of 20 cc. 20 per cent magnesium sulphate in man has no significant effect on the normal conducting system. In paroxysmal tachycardia, however, it sometimes restores sinus rhythm or it may produce variable degrees of heart block. The drug seems to depress impulse production in heterotopic centres. Bachrach (91) reports that magnesium chloride solution slows the heart and increases diastolic relaxation in the isolated ventricle of *Helix.*

Metabolism.—The cat heart has now been shown to metabolize acetic acid. When sodium acetate containing radioactive C in the carboxyl group was added to the circuit of the blood perfused isolated cat's heart, it was readily converted into carbon dioxide as indicated by the appearance of radioactive C in the respiratory carbon dioxide up to 31.5 per cent of the total respiratory carbon

dioxide was derived from administered sodium acetate [Lorber *et al.* (92)]. Similar experiments with glycine showed that this was only very slightly metabolized, yielding only 0.5 per cent of the total carbon dioxide output as contrasted with acetate [Lorber & Olsen (93)]. Lackey, Bunde & Harris (94) kept adult male rats on diets producing different blood ketone levels. Samples of blood were analysed for sugar, ketones and lactate, while liver, heart and muscle glycogen were also estimated. There is a direct correlation between cardiac glycogen and ketones, but none between glycogen and blood sugar or lactate.

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PERIPHERAL CIRCULATION

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The present review was written with two purposes in mind. The first was to discuss critically some of the newer concepts which are of basic importance for an adequate understanding of the functional activity of the peripheral vascular apparatus. Only recent references bearing on the subject have been included, no attempt being made to review completely the work in these categories. The second aim was to compile the pertinent literature relating to the field as a whole, covering the period from July 1946 to July 1947. Although shock and hypertension are discussed elsewhere in this volume, it was thought best to include here sections on these topics in order to emphasize the vascular phenomena characteristic of these conditions.

Methods of Study

Improved methods for direct measurement of arterial blood pressure have been described (1, 2). The Clark pressure capsule, which records fluctuations in pressure by changes in the magnetic reluctance of a crystal, was tested by Motley, Cournand and co-workers (3) in man and was found to be a reliable and somewhat more flexible instrument than the conventional Hamilton manometer. Modifications of the catheterization technique have made it possible to obtain more accurate recordings of right atrial and ventricular pressures [Cournand *et al.* (4)], of changes in the pulmonary arterial circulation [Dexter and co-workers (5)], and of hepatic blood flow [Bradley (6)].

Despite its many inadequacies, the method of direct visualization of the peripheral circulation still offers the most satisfactory means for differentiating between the reactions of the several components of the vascular bed under varying experimental conditions. Chambers & Zweifach (7) listed the precautions for maintaining the normal state of vascular reactivity in tissues exposed for

[1] I would like to express appreciation to Miss Delilah B. Metz for her co-operation in compiling the references and bibliography and for her valuable assistance in abstracting many of the articles.

microscopic study. Fulton, Jackson & Lutz (8) have observed the peripheral blood vessels of the hamster by exteriorizing the cheek pouch, a semitransparent structure readily prepared for microscopic study with a minimum of trauma.

Burch (9) described a plethysmographic technique sufficiently delicate to distinguish variations in flow and in wave patterns of the terminal arterioles in the digits of man and animals. Long (10) adapted a perfusion method to study circulatory changes in organs such as the stomach, pancreas and spleen *in situ*. Binet & Burstein (11) were able by a cross-transfusion technique to measure separately the peripheral and central effects of various agents on the terminal blood vessels.

Chambers & Zweifach (12) found it possible to use the highly sensitive responses of the terminal arterioles and precapillaries in the mesoappendix (preferably mesocecum) of the rat as a means for the detection and the assay of vasotropic substances in blood and tissue extracts. The intravenous injection of such substances into the test rat produced a transient change in the reactivity of the peripheral vascular components to the topical application of epinephrine. This enabled them to quantitate the vasoexcitor or vasodepressor activity of different samples, either on the basis of the duration of the effect, or by the degree of change in the concentration of epinephrine necessary to reproduce the control type of vasoconstriction.

Other studies of the peripheral circulation are those of Ray (13) who used changes in the reduction time of oxyhemoglobin, and of Smith & Quimby (14) who followed the distribution of radioactive sodium. The development of capillary petechiae under different conditions was analyzed by direct capillary microscopy in the human skin [Davis (15)], and in the rabbit eye [Chambers & Copley (16)]. Gibson and co-workers (17) incorporated radioactive isotopes of iron into red blood cells as a means for determining not only an absolute measure of the circulating red cells but the total volume of circulating blood when used in combination with the T-1824 plasma volume technique.

Bazett (18) described a mechanical schema by means of which the effects of variations in venous and arterial blood flow on the capillary circulation could be studied. Branson (19) claimed that mathematical equations for the flow of a viscous fluid in an elastic tube could be applied for flow in the femoral artery.

Architectural Pattern of Peripheral Vascular Bed

The terminal ramifications of the arterial tree, the arterioles, precapillaries, capillaries and venules, constitute an organic unit, the capacity of which is constantly being varied by changes in the number of vessels containing an active flow (20). The muscular components of the terminal vascular bed are arranged so that a progressive restriction of blood flow occurs without interrupting the continuous flow to the veins through centrally located, preferential channels. In certain tissues, such as the mesentery and the omentum, the preferential channels are structurally differentiated from the remainder of the capillary bed. In other tissues, the proximal muscular portion of the preferential channel is well differentiated, but the distal continuation into the venules varied with the conditions of flow. Direct capillary channels of this nature have been described by many of the earlier workers in the field, and recently by Crismon & Fuhrman (21) in the circulation of the rabbit ear under normal conditions. Nicoll & Webb (22) could detect no anatomically differentiated preferential channels in the capillary bed in the wing of the bat. They did find on the arterial side of the bed, muscular capillary channels with the typical precapillary sphincters guarding the exit into the network of true capillaries. The precise distribution of these preferential channels in different tissues needs further systematic investigation.

Vasomotion

Direct visualization of the capillary bed has indicated a periodic narrowing and partial dilatation of the terminal arterioles and precapillaries which occurred independently of the larger blood vessels under normal conditions and which showed characteristic variations under abnormal conditions (20). Nicoll & Webb (22) described a prominent vasomotion in the veins of the bat's wing. This has not been observed in other tissues and may represent a specialized function in the wing to aid the return of blood from the tissue. An analysis of plethysmograph records of blood flow in the digits of humans indicates changes in wave patterns which appeared to correspond to peripheral vasomotion (9). Similarly, the intermittent uptake of lymph fluid and the changes in interstitial pressure described by McMaster (23) may be related to peripheral vasomotion. Vasomotion appears to be influenced by both nervous factors and tonic influences of local tissue and of humoral origin.

Zweifach (24) found that complete denervation of the blood vessels in the tongue of the frog disrupted the periodicity of the vasomotor activity, the vessels remaining in a partially contracted state. Nicoll & Webb (22) found that denervation of the bat wing did not interrupt the irregular vasomotion of the terminal arterioles and precapillaries. It was not stated whether their denervation procedure was sufficiently complete to eliminate all sympathetic fibers or to what extent the vascular changes could be attributed to local axon reflexes.

Fulton & Lutz (25) used microelectrodes to stimulate the delicate nerves in the capillary bed of the retrolingual membrane of the pithed frog. They concluded that separate constrictor and dilator nerves were distributed to the arterioles and junctional precapillaries of the bed. No active changes in the caliber of the nonmuscular true capillaries were seen. The possible existence of a dual innervation warrants further investigation, especially since, in the experiments of Fulton & Lutz, the vasomotion of the arterioles and precapillaries had been abolished by pithing of the spinal cord. Zweifach (26) and Nicoll & Webb (22) have demonstrated by vital staining with methylene blue a delicate nerve net intermingled with the capillary vessels but could find no evidence of an innervation of these purely endothelial structures. In unanesthetized animals (22, 27) there occurred a sudden and intense peripheral vasoconstriction, which included the arterioles and precapillaries whenever the animal struggled or was subjected to a painful stimulus. The caliber of the true capillaries remained unaffected. This is indirect evidence for the absence of a nervous control of the true capillaries. Fulton & Lutz (25), and Nicoll & Webb (22) attempted to distinguish between changes in blood flow mediated by sympathetic nerve stimuli and those resulting from the inherent tone of the smooth muscle cells. Such a distinction is not readily made since both factors can be similarly affected by local environmental conditions.

Capillary Wall

Relatively few studies have been made on the finer cytology of the endothelial cell. Recently, Roskin (28) described the presence of a perinuclear Golgi apparatus in the capillary endothelial cells and the absence of stainable glycogen. The terminal ramifications of the arterioles up to and including the precapillary sphincters

possess well-defined muscle cells many of which are branched and are probably the cells referred to by Krogh, Vimtrup and others as Rouget cells. No such muscle elements were found on the true capillaries (29) which are purely endothelial. Knisley (30) stated that the capillary endothelium of the frog and other amphibia was definitely contractile, a finding not confirmed by others. Unless the capillary wall is clearly visible, claims for endothelial contractility must be made with caution, especially since the endothelial wall is difficult or impossible to make out even in transparent tissues when devoid of circulating blood cells. Vasoconstrictor drugs, when applied to the surface of tissues, produced a constriction only of the muscular components of the capillary bed. Observations have been made on the vessels in the skin, skeletal muscle, omentum and intestinal wall of rat, cat and dog and the application of epinephrine in no instance produced a contraction of the endothelial wall (31).

Permeability of Capillaries

In a recent review of the subject Chambers & Zweifach (32) stress the structural features of the capillary wall concerned with the interchange of material between the blood and the tissue spaces. Variations in permeability of the capillary could be accounted for by changes in the nonliving components of the vessel wall. The bulk of the interchange between blood and tissue occurred between the endothelial cell rather than through the cell body. The interendothelial cement is a porous structure upon which there is adsorbed a layer of blood protein which, by filling the porous interstices of the cement, serves further to regulate the porosity of the membrane. Another constituent was the closely adhering pericapillary sheath, a condensation of the connective tissue matrix. The balance of fluid exchange was considered to be maintained not so much by a direct interplay of hydrostatic and colloidal pressure as by delicate vasomotor adjustments which intermittently increased or decreased the surface area over which outward filtration occurred. In this regard changes in peripheral vasomotion of the arterioles and precapillaries were of major importance. Along with this constantly shifting balance of the hemodynamics are changes in the physicochemical composition of the several structures which constitute the wall of the capillary. Each of these components could be altered separately by a variety of

conditions, making it impossible for a single permeability factor to account for the stability of the membrane barrier between the blood and the tissues.

Chambers and Zweifach believe that the outward filtration of fluid from the blood occurred chiefly along the preferential channels between the arterioles and venules. Inward filtration occurred largely along the extensive network of true capillaries, in which there were considerable variations in flow and in pressure, chiefly as a result of the vasomotion of the precapillary sphincters. It is interesting to note that Crismon & Fuhrman (21) could best explain the vascular and edema changes which occurred in the rabbit ear after frostbite on the basis of this concept. They found that the blood flow in injured regions persisted through thoroughfare channels. The persistence of edema could best be ascribed to a decrease in the capillary surface available for inward diffusion while outward filtration continued along the injured thoroughfare channels.

Histamine and leukotaxine have been found to increase the permeability of the capillary wall. Lehmann *et al.* (33) and Bonvallet & Decourt (34) found that it was possible by pretreatment with an antihistamine agent to prevent the edema and local accumulation of T-1824 following the intradermal injection of histamine. However, the intravenous administration of an antihistamine agent (neoanteragan), which prevented the increase in capillary permeability produced by histamine, was found to have no effect on either the burn edema or on the edema produced by leukotaxine injected into the skin (35). Last & Loew (36) in a study of the action of benadryl and neoantergan have presented evidence disproving the contention that histamine is the major factor in the increased permeability associated with agents such as snake venom, trypsin, sensitized serum, etc.

Abell (37) has confirmed previous findings that the newly formed capillaries in the rabbit ear chamber are more permeable to the dye T-1824 than adult capillaries. He assumed that the dye, which appeared outside the capillary, represented the leakage of plasma protein to which the T-1824 had become bound.

Recently, it has been shown that edema does occur despite the absence of changes in the relative concentration of the blood colloids. Keys and co-workers (38) found that edema developed during starvation although the plasma protein levels remained relatively unchanged. Ralli and associates (39) found in cirrhotic pa-

tients that ascites and edema developed with no corresponding changes in the plasma proteins. These experiments point to the presence of factors other than osmotic for maintaining normal permeability relationships. They presumably serve to keep the capillary wall in a relatively stable physicochemical state.

Soto-Rivera & Pappenheimer (40) using a hind-limb perfusion technique, with carefully controlled conditions, studied the capillary-tissue fluid exchange by measuring the rate of weight change. Their method enabled them to arrive at the isogravimetric capillary pressure, the pressure at which filtration and absorption counterbalance one another. This value was found to be independent of the absolute value of the colloid osmotic pressure. More pronounced changes in capillary filtration were produced by changing the arterial pressure while keeping the venous flow constant than were obtained by changing the venous pressure while keeping the arterial flow constant. These comparative values, however, hold for the *in vitro* hind leg system and may not be as significant in the intact organism where compensatory mechanisms are in operation.

Brown & Landis (41) studied the permeability effects of cooling the mesentery of the frog to between -2 C. to $+2$ C. The filtration constant, as estimated by movement of the blood cells in vessels occluded with a microneedle, was reduced about 73 per cent, indicating a markedly decreased capillary permeability. The results obtained by them can be explained by changes produced by the cold on the physical state and porosity of the interendothelial cement.

Frostbite.—Quintanilla, Krusen & Essex (42) found that frostbite made the capillaries in the rabbit ear chamber completely permeable to the blood plasma, the rapid egress of fluid leaving behind conglomerate masses of cells in the vessel. Friedman and co-workers (43) showed that heparin did not prevent the intravascular agglutination of red blood cells in experimental frostbite. The vascular stasis and occlusion in these experiments would appear to be the result of direct injury to the capillary endothelium causing the cells to shrink away from one another and allowing the plasma to be filtered off into the tissue. When sheets of epithelium or kidney tubules were exposed to cold (12° to 14° C.), the cells shrank away from one another but remained viable (44). A similar change was also obtained by Chambers (45) in the capillaries of the frog following the application of hypertonic saline. The

endothelial cells shrank away from one another making the capillary highly pervious so that the plasma leaked out and left only the blood cells within the lumen of the capillary.

Crismon & Fuhrman (46, 47, 48) in studies on cold injury found that during the production of frostbite there occurred an initial hyperemia and vascular dilatation followed by stasis in the true capillaries. There developed an apparently paradoxical situation, namely, a relatively slow appearance of fluorescein in the injured tissue despite the presence of an increased total blood flow immediately following the injury. They believed that a rapid blood flow continued in the injured region through thoroughfare channels, thereby permitting outward filtration. Stasis in the true capillaries limited the area available for diffusion and could account for the relatively slow penetration of the fluorescein into the injured tissue.

Capillary fragility.—The capillary wall under abnormal conditions becomes sufficiently pervious to permit the extravasation of blood cells into the tissues. Chambers & Cameron (49) have found that the absence of ascorbic acid had no effect on the intercellular cement substance in tissue culture preparations. The increased fragility which occurs in scorbutic animals and patients appeared to be due to a weakening of the pericapillary connective tissue matrix (50). Lee & Lee (27) described petechial hemorrhages in the mesentery of scorbutic guinea pigs, especially in the small venules. Chambers & Copley (16) have observed similar changes in the vessels of the rabbit eye following the application of irritants. Various agents, among them rutin (51, 52), vitamin P and vitamin C (53, 54) have been claimed to exert a protective action against the development of increased capillary fragility under different conditions. Parrot & Cotereau (55) postulated that both vitamin P and ascorbic acid were essential for the maintenance of normal capillary fragility and that the development of an antivitamin P factor may lead to an increased capillary fragility.

Griffith *et al.* (56) described an increase in capillary fragility following exposure of the peritoneal cavity of the rat to irradiation. Whether this represented an increased capillary permeability or a degeneration of the surrounding connective tissue matrix could not be determined. Chambers & Cameron (57) found that tissues cultured *in vitro* were far more resistant to x-rays than the same tissues irradiated in the body. Even when excessive doses of x-ray

were used (100,000 Roentgen units) no effect on the viability of the cell was discernible. Chick kidney cysts in tissue culture actively secreted fluid into the lumen of the cyst distending it even to the point where the cuboidal epithelium becomes distorted to flat pavement-like cells. When such preparations were exposed to x-rays, the cysts no longer retained fluid and collapsed. This effect was completely reversible. It would therefore appear from *in vitro* experiments that the action of the x-rays was to weaken the intercellular cement substance. The increased susceptibiility of tissues to x-rays in the animal may be related to a similar action on the interendothelial cement.

Blood Flow in Tissues

Gibson and co-workers (58), by means of radioactive iron incorporated in red blood cells and iodine incorporated in the plasma protein, followed the intravascular distribution of blood in the different tissues of the body. In normal dogs, maintained under light morphine narcosis, only 17 per cent of the total blood volume was present within the arterioles, capillaries and venules, the largest fraction of this being in the liver and skeletal muscles. Their data would appear to indicate that there were no reserves of red cells in the normal dog. Wilkins & Bradley (59) stated that the changes in blood flow and pressure distal to a cuff occluding the arm make it possible to determine whether there were free communications between the arteries and capillaries. Dripps & Comroe (60) believed that the abrupt fall in diastolic blood pressure at the termination of inhalation of carbon dioxide was more probably due to a sudden withdrawal of a vasoconstrictor effect of reflex origin than to a direct stimulating effect on the vasomotor center.

Intrarenal hemodynamics have been studied by a number of techniques. Selkurt (61) made direct measurements of blood flow from the renal vein and found that moderate fluctuations in arterial pressure produced changes in renal blood flow which did not appear to be related to a specific regulatory mechanism of a vasomotor type. On the other hand, Barclay, Trueta and co-workers (62, 63) have compiled evidence for the existence of a reflex mechanism which short-circuited the blood from the cortex to the medulla of the kidney. This could occur to any degree up to complete cortical ischemia. They believed this mechanism to be operative in a

wide variety of conditions such as those produced by noxious agents, or by hemorrhage and speculated that renal anoxia of this type may occur in hypertension. The evidence of Phillips *et al.* (64), based on the extraction of diodrast or para-aminohippurate from the renal blood during experimental shock, does not appear to support the above findings. The experiments of Selkurt (61), indicating a dissociation between renal blood flow as measured directly and plasma flow as determined by the clearance methods, show how difficult it is to draw conclusions from data obtained by different techniques.

Barcroft & Edholm (65, 66), in an investigation of vasoconstrictor tone of the blood vessels in human skeletal muscle during syncope, found a vasodilatation in the muscles at the time that the blood pressure fell abruptly. Their argument for an active vasodilatation was based on the finding that nerve block produced a decreased flow in the muscles of the forearm. This procedure may merely produce a redistribution of blood through the muscles and not an increased vasoconstriction.

Allen, Barcroft & Edholm (67) observed a transient dilatation followed by a vasoconstriction in the human arm during a constant infusion of epinephrine. This occurred both in normal individuals and in sympathectomized patients. They attributed this biphasic effect to an initial capillary dilatation followed by arteriolar constriction. Nylin (68), using red blood corpuscles tagged with radioactive phosphorous, could find no evidence for the participation of a blood reservoir which increased the circulating blood volume during muscular work. Brun (69) measured changes induced by intravenous epinephrine in the omental and gastric arteries following local anesthesia of the vessel wall proximal to and including the region under observation. He concluded that the degree of contraction was in large part controlled by reflexes originating locally in the sympathetic nervous system. Bürgi (70) described an "organized" spontaneous rhythm of the peripheral arteries and arterioles which was affected in a characteristic way by different vasoconstrictor drugs. Gubner, Di Palma & Moore (71) found that it was possible to increase the blood flow through the skin by the feeding of glycine, apparently as a result of the specific dynamic action of the substance and the consequent increase in body temperature.

Vasomotor Reactions

Holt and co-workers (72) made an analysis of the factors concerned with reflex vasomotor changes of the arterial blood pressure. They came to the conclusion that the regulation of arterial blood pressure was for the most part mediated by changes in cardiac output and to a lesser extent by peripheral vasoconstriction. Sarnoff & Simeone (73) could find no evidence for the existence of vasodilator nerves to the vessels in the human skin. A major argument for this conclusion was the finding that, at the height of the elevation of skin temperature brought about by reflex vasodilatation, nerve block did not produce a fall in skin temperature.

Disagreement exists on the factors concerned with the regulation of the circulation during muscular work. Asmussen, Nielsen & Wieth-Pedersen (74) concluded that the regulation of the circulation during exercise was probably governed reflexly by sensory impulses arising within the working muscles and acting either upon the vasomotor center or on the adrenals. Von Euler & Liljestrand (75) assigned a prominent role in the regulation of the blood pressure during work to the baroreceptors, since denervation of these zones by thoracolumbar sympathectomy was followed by a fall in diastolic pressure during work.

Heymans *et al.* (76, 77) studied the effects of calcium and magnesium ions, and alcoholism on the carotid sinus reflexes. They (78, 79) also found that DFP (di-isopropylfluorphosphate), which completely blocks blood cholinesterase activity, had no effect on carotid sinus reflexes initiated by an increased or decreased pressure within the sinus. It should be emphasized that the tissue level of cholinesterase does not necessarily correspond to the level of cholinesterase in the blood. Nathanson (80) studied the circulatory changes in patients with a hyperactive carotid sinus reflex. He found that atropine abolished the cardioinhibitory effect but did not alter the vasodepressor effect which occurred with sinus stimulation, and concluded that either the vagus center in the medulla or efferent fibers in the vagus must be responsible for the hyperactivity of the carotid sinus reflex. Conklin (81) showed that reflex circulatory compensation occurred during hypotension even after the carotid sinus and aortic nerves have been eliminated. Emphasis was placed on the value of the respiratory pumping action as an agency promoting the venous return from the hind limbs

and splanchnic regions during stress. Dern & Fenn (82) and von Euler & Liljestrand (83) studied the relation of arterial pressure to changes in the pulmonary pressure. They found that the arterial pressure was influenced by changes in intrapleural pressure, the changes being a combination of mechanical factors and reflex effects on the blood pressure regulatory receptors.

Holmgren & Silfverskiöld (84) cited evidence that the variations in the volume of the vena cava were independent of those of the peripheral veins and that caval changes did not occur passively as a result of mechanical collapse or stasis. Burstein (85) perfused the lobe of a lung *in situ* and studied the changes in pulmonary blood flow. Stimulation of the stellate ganglion, the peripheral end of vagosympathetic trunk, the carotid sinus, or hemorrhage, had almost no effect on pulmonary blood flow. Local reflexes within the lung as a result of emboli in the pulmonary blood vessels or intratracheal hypertension, produced the greatest changes in pulmonary circulation.

Meneely *et al.* (86) found that the only significant circulatory change after convalescence was an increase in venous pressure. Deitrick & Whedon (87) found a significantly decreased venous return of blood from the legs and an increased tendency to faint on the tilt table in patients who had been immobolized in bed. The use of an oscillating bed tended to counteract the deterioration of the vasomotor control exhibited by these patients in the upright position.

Heymans & Delaunois (88) presented evidence that moderate anoxia or hypotension of the vasomotor center had no direct effect on its activity, whereas similar conditions in the carotid sinus served to stimulate reflexly the vasomotor center. They believed the restoration of blood flow to the vasomotor center, following a period of prolonged hypotension, actually depressed its tone and suggested that this phenomenon was related to the development in shocked animals of a depressed vascular state after unsuccessful transfusion. Hyperventilation, alkalosis or acapnia did not depress the carotid sinus reflex (89).

Lee & Lee (27) made a study of the changes in the reactivity of the mesenteric blood vessels in guinea pigs subjected to experimental scurvy. A characteristic finding was the development of marked hypotonia which involved not only vascular dilatation but a refractoriness of the terminal arterioles and precapillaries to

epinephrine. Petechial hemorrhages appeared after vascular hypotonia had developed.

Tissue Derivatives

A number of antihistamine compounds have been developed which, although they counteract the local action of histamine, vary in their ability to inhibit the vasodepressor response to histamine [Marsh & Davis (90)]. Antihistamine agents have also been found to counteract the depressor effects of acetylcholine (91) and to enhance the pressor response to epinephrine (92). Wirtschafter & Widmann (93) injected sodium ascorbate and histidine with the view towards forming histamine *in vivo* in patients with impaired circulation in their extremities. Evidence for the appearance of histamine in the urine and blood was deduced from the histamine-like contraction of the guinea pig intestine which these samples produced.

De Waele & Van de Velde (94) found that adenosine triphosphate produced a dilatation of the abdominal and skeletal blood vessels but had no effect on the kidney or spleen. Ungar (95) presented evidence for the participation of a spleen derivative, splenin, in the response of the vascular system to conditions of stress. He believed that splenin increased the antitryptic action of the blood and thereby inhibited the liberation of vasodilator protein breakdown products. The fact that the spleen undergoes maximal contraction early in shock and that splenectomized dogs subjected to shock differ in no significant way from normal dogs, would seem to minimize the protective role of the spleen in these conditions. Von Euler (96, 97) extracted from different mammalian tissues, especially heart, a pressor substance which resembled epinephrine in its peripheral vascular effects but which differed from it chemically. He believed the substance to be noradrenaline or some closely allied compound.

Shorr, Zweifach & Furchgott (98) have described a hepatic vasodepressor principle which inhibited the reaction of the terminal arterioles and precapillaries to epinephrine. This principle (VDM) appeared in the blood during the latter stages of shock and brought about a decompensatory set of changes in the peripheral blood vessels. VDM was prepared from liver tissue subjected to anaerobiosis *in vitro* and has been concentrated to a state of high purification [Mazur & Shorr (99)]. Baez *et al.* (100) analyzed the

disappearance of vasodepressor material from the blood following its intravenous injection into rabbits. Both the liver and kidney were found necessary for the removal of VDM from the bloodstream. When the liver was excluded, leaving only the kidney in circulation, the VDM was found to be excreted into the urine. When the kidneys were occluded, leaving only the liver in the circulation, the VDM disappeared from the blood but somewhat more slowly than in hepatectomized animals. When both the liver and kidney were excluded from circulation, the injected VDM remained in the bloodstream throughout the period of observation.

Zucker (101) made direct observations on the mesenteric circulation in rats and observed the constriction of blood vessels around the site of an injured area. This was attributed to the liberation from platelets of a vasoconstrictor substance. When heparin or dicoumarol was injected into the bloodstream prior to trauma, no intravascular platelet plugs were formed and no vasoconstriction of nearby vessels was seen. The evidence does not rule out the possibility that the continued bleeding following heparinization or dicoumarol may wash away any potential vasoconstrictor substances produced by the vascular injury.

Drugs and Hormones

Hormones.—Whether the impairment of the peripheral circulation, which results from adrenalectomy, is a consequence of reduced "capillary" tone or is secondary to disturbances in electrolyte balance, remains controversial. Clarke *et al.* (102) made a detailed study of the circulatory factors related to adrenal insufficiency and concluded that the reduction in circulating plasma volume which occurred was insufficient to account for the circulatory collapse during crisis. There occurred a slow but considerable loss of protein, especially albumin, from the circulation. They were unable to ascertain whether the capillary changes were a result of disturbances of the blood electrolyte balance or a manifestation of a direct protective action of the cortical hormones on the capillaries.

Overman & Feldman (103) found no changes in the circulation of the monkey with seasonal variations in the extracellular fluid volume. Synthetic estradiols were used by McGrath & Herrmann (104) to improve peripheral vasomotor tone. They attributed the prolonged dilatation, resulting from intramuscular injection of estrogen, to a liberation of acetylcholine-like substances in the

tissues. Kaiser (105), on the other hand, found that estrogens produced in endometrial occular transplants a considerable dilatation and an increase in the number of functional capillaries. Since these vascular changes were not affected by atropine, the acetylcholine action of estrogens would appear to be ruled out. Woodbury & Ahlquist (106) believed that the increased cutaneous flow which is produced by pitressin could be attributed two factors: a passive effect from an elevation of the arterial pressure, and an active change resulting from a dilatation of the cutaneous vessels.

Griffith *et al.* (107) found that the intravenous administration of epinephrine produced either an increase or decrease in blood flow through the limb of the cat depending on the rate of injection. The pressor effect seemed to be related to the output of lactate and the oxygen consumption of the tissue. Kumpas (108) found that the vasoconstrictor and depressor effects of epinephrine were enhanced following section of the buffer nerves. McDowall (109) attempted to analyze the potentiating action of acetylcholine on the vasoconstrictor action of epinephrine. A similar potentiation was obtained on the perfused vessels of isolated hind-limbs indicating that the synergism was not related to a stimulation of sympathetic ganglia. Dawes (110) studied the differences in the vascular response to epinephrine when injected into the portal vein and into the jugular vein. He found that various diamidines reduced the inactivation of epinephrine by the liver so that the two routes of injection now produced almost similar vascular effects.

Danilopolu (111) found that the administration of acetylcholine after atropinization produced a vasoconstriction and a rise in blood pressure, which could be abolished by adrenalectomy. Although atropine blocked the direct vasodilator effect of acetylcholine on the blood vessels, the vasoconstriction which occurred was explained by him to be the result of the stimulating action of acetylcholine on the secretion of epinephrine by the adrenal gland.

Drugs.—Within recent years a considerable number of adrenolytic and sympatholytic agents have been developed. Amongst these, priscol and dibenamine have been extensively studied. Priscol has been found (112) to produce a differential sympathetic depression and a reversal of the vascular response to epinephrine. Nickerson & Goodman (113) found that the adrenolytic and sympatholytic effects of dibenamine occurred at different concentration levels. The sympatholytic action was less consistent, es-

pecially in relation to contraction of splanchnic blood vessels. The site of action of this drug remains obscure. Haimovici (114) found that dibenamine neutralized the vasoconstrictor effects of epinephrine on the isolated perfused blood vessels of the frog hind-limb. Hypertensin and nicotine continued to produce a vasoconstriction despite the complete blockage of epinephrine effects. Verlakov (115) described a powerful epinephrine antagonist which was of plant origin and which produced *in vivo* a pronounced fall in blood pressure and renal vasodilatation.

Various investigators have found that anesthetic agents interfered with peripheral vasoconstriction (116, 117). Lorhan & Mosser (118) were able to counteract the vasodilatation produced by spinal anesthesia with phenylpropanolamine, a relative nontoxic vasoconstrictor agent whose action resembles that of epinephrine but has a more prolonged effect. Zweifach *et al.* (119) found that anesthetic agents, such as ether or pentobarbital, depressed the response of the terminal arterioles to epinephrine. Other agents, such as cyclopropane and morphine, enhanced the reactivity of the peripheral blood vessels to epinephrine. The peripheral circulation in dogs anesthetized with cyclopropane was found to resemble most closely the condition observed in unanesthetized animals. Cyclopropane was the only anesthetic agent which did not predispose to the formation of vasodepressor substances during hemorrhagic shock.

The drug, tetraethylammonium chloride (TEA) has been used extensively in the treatment of peripheral vascular disease (120). Acheson & Moe (121) found that TEA produced a drop in both systolic and diastolic blood pressure as a result of a block of efferent pathways in sympathetic ganglia. The drug did not affect the response to epinephrine in either normal or cord-transected animals. The effect of TEA on sympathetic ganglia could be blocked by prostigmine (122). The injection of TEA produced a transient increase in blood flow in the extremities, somewhat less pronounced than that resulting from sympathetic block (123).

Fastier & Smirk (124) studied the circulatory effects of various vasoconstrictor agents, among them isothiourea, guanidine and various amidines. These agents produced vasoconstriction in the perfused hind-limbs of the pithed rat even after the administration of ergotoxin. They also sensitized the blood vessels to epinephrine. Bovet & Bovet-Nitti (125) believed that the nitric ester of

aminoethanol, and a number of its derivatives, produced a hypotensive effect by virtue of a diminution in tone, specifically of the arterioles and muscular capillaries of the skin and lungs. Lands and associates (126) studied the action of various vasodepressor amines which were structurally similar to the sympathomimetic amines and found that these depressor agents produced their most pronounced vascular effects in those organs which showed an inhibitory response to epinephrine.

Patt and co-workers (127), and Cameron & Courtice (128) found that fatal pulmonary irritant poisoning was not due to a collapse of the peripheral circulation but was primarily a result of an interference with oxygen uptake through the edematous lungs. Chenoweth (129) found that the fall in systemic blood pressure produced by BAL (2, 3 dimercaptopropanol) was accompanied by a pooling of blood in the liver and splanchnic areas and by a marked rise in the peripheral resistance of the limb vessels. The increased peripheral resistance in the limb vessels observed by Chenoweth is probably a compensatory response to the selective withdrawal of blood from the active circulation into the splanchnic area. Hitchcock (130), in his studies on the effects of BAL and related substances, also found that the blood vessels of various organs reacted differently to such enzyme inhibitors.

Hypertension

The increased use of the rat in studies on experimental hypertension has led to the development of new procedures for the production of hypertension in these animals, viz., audiogenic stimulation of susceptible strains of rats (131), perinephritis induced by latex molds about the kidney (132), partial constriction of the aorta above the kidney just sufficient to depress glomerular filtration in conjunction with occlusion of the ureter (133), and arterial ligation and partial infarction of the kidney (134). Sulkin & Brizzee (135) cautioned against the use of anesthetic agents to facilitate the determination of blood pressures in the rat. Bouckaert & de Landsheere (136) described a new technique for obtaining renal vein blood in animals without disturbing the position of the kidney. Victor (137) produced a sustained hypertension in dogs by the partial occlusion of the circulation to the adrenal gland. At a recent conference on hypertension, Goldblatt, Ogden & Wakerlin (138) reported their inability to produce hypertension

by this procedure. Moss & Wakerlin (139) in studies on hypertensive dogs were unable to corroborate the findings of Ogden and coworkers (140) on rats, indicating an initial phase related to humoral factor of renal origin and a subsequent phase involving an alteration in the sympathetic nervous system which then sustains the hypertensive condition.

Russian investigators have emphasized changes in the capillary bed as of primary significance in the etiology of hypertension. Gorev & Smirnova-Zamkova (141, 142) pointed out that the earliest histological changes during the development of neurogenic hypertension occurred in the argyrophilic substance of the pericapillary sheath. During the development of hypertension the normally amorphous ground substance of the pericapillary sheath showed the presence of delicate fibrils which progressively lost their identity and fused to form collagen. Although the initial changes were found to be reversible, the latter led to nonreversible fibrosis. Kogan-Yasny (143) presented a classification of hypertension based on (*a*) local tissue humoral changes; (*b*) circulating pressor substances in the blood; (*c*) changes in the vessel wall. He stated that the repeated injection of hypertensive serum into rabbits produced an elevation of blood pressure which persisted for almost nine months. Significant pathologic changes were observed in the hypophysis of hypertensive animals and patients. He concluded that the initiating factor in hypertension was neurohumoral in origin and that subsequent changes in the vessel wall were a secondary development. He quoted Gelfgat who made microscopic observations on the blood vessels of hypertensive patients and found irregularities in blood flow and vascular spasm considerably before the development of organic changes in the blood vessels.

Selye & Stone (144) were able to produce pathological changes, similar to those obtained in malignant hypertension by the administration of DCA and salt, testosterone, or adrenocorticotropic hormone. They believe that these factors have an etiological role in hypertension. Among the changes described was a swelling and development of granules in the cells of the juxtaglomerular apparatus previously emphasized by Goormaghtigh (145). Dunihue (146) found that renal hypertension produced a hypertrophy and increase in the granular cells of the juxtaglomerular apparatus. He also observed that following bilateral adrenalectomy a small pro-

portion of the animals survived for more than one week, and that the juxtaglomerular apparatus of these survivors had undergone hypertrophy. Schloss (147) recently made a detailed study of the changes in the epithelioid cells in the wall of the afferent arterioles of the kidney. He concluded that these cells probably acted as secretory cells and not as cells whose swelling per se produced a narrowing of the arteriolar vessels. Whether the juxtaglomerular cells represent the site of origin of the renal principle associated with experimental hypertension cannot be clearly determined from the present evidence.

Freedman & Freedman (148) suggested that a chronic deficiency of a hyaluronidase factor might produce changes in the blood capillary wall which would necessitate a compensatory increase in blood pressure to maintain fluid exchange between the blood and tissues. Their evidence in support of this concept was inadequate. Halpert & Grollman (149) found that hypertension produced by renal ligatures resulted in the appearance of diffuse lesions in the damaged kidney and focal lesions in the intact kidney, with no evident changes in the arteries of other tissues.

The occurrence of an increased amount of renin in the blood following acute damage to the kidney was explained by Bing (150) as being due to the increased permeability of the cell membrane to renin. This would indicate that renin was an intracellular constituent which reached in the blood only under abnormal conditions. Zweifach, Shorr & Baez (151, 152, 153) have recently reported a series of experiments dealing with renal hypertension in dogs and rats in which they found that intact kidney cells produced a vasoexcitor principle (VEM) which appeared in the bloodstream during the development of hypertension. This substance differed from angiotonin or hypertensin in not having a direct musculotropic action and in being produced by the kidney *in vitro* in the absence of any blood plasma component. The presence of the VEM principle was detected by the rat mesoappendix method of assay (12), the vasoexcitor principle having a potentiating effect on the reactions of the terminal arteriole and precapillaries in the mesentery to the topical application of epinephrine. Blood removed during the chronic stage, two to three months after the establishment of a sustained hypertension, was found to have no effect on the blood vessels of the test rat. Shorr *et al.* (154) were able to show that the VEM in the blood had its origin in the kidney to which a Goldblatt

clamp had been applied. Normal kidneys produced VEM *in vitro* only under anerobic conditions. In contrast, within five hours after partial constriction of the renal artery, the kidneys were transformed into organs which elaborated VEM under completely aerobic conditions. Since this effect was obtained with kidneys removed from hypertensive dogs as long as nine to ten months after the clamp had been applied, there appeared to be a discrepancy between the continuous formation of VEM by the kidneys and the absence of a demonstrable vasoexcitor effect in the blood of these animals. The "neutral" rat test given by these blood samples was found by Shorr, Zweifach *et al.* (98) to represent a corresponding increase in the blood level of the oppositely acting vasodepressor principle, VDM.

Recently Shipley and associates (155) have described a hypertensive principle which they obtained from the blood of animals which died after a moderately prolonged period of hypotension. When injected into nephrectomized pithed cats, the blood samples produced a sustained elevation in blood pressure. The substance does not appear to be related to renin and has not been demonstrated in the blood of hypertensive animals.

Shaw (156) and Goldblatt (157) reviewed the evidence supporting the involvement of the kidney as a factor in the etiology of human essential hypertension. Shaw believed that the primary change in essential hypertension was the development of an imbalance between the adrenal glands and the vascular sympathetic system, leading to an increased sensitivity of the neuromuscular effector unit of the terminal blood vessels. This appeared to occur by virtue of a disturbance in the adrenal cortex affecting the metabolism and excretion of electrolytes. Øster (158) cited the case of a seven-year-old boy who had developed a pronounced hypertension after ligation of an aberrant renal artery and which was relieved by nephrectomy. The case was of further interest since it illustrated a sustained hypertension with only unilateral renal involvement.

The recent work of Shorr, Zweifach and co-workers (154) on changes in the VEM formation mechanism illustrated how a specific metabolic defect could occur in the kidney without demonstrable changes in the functional capacity of the kidney, as indicated by renal clearance studies. This made untenable the conten-

tion of Goldring & Chasis (159) that the failure to demonstrate functional alterations in the kidney ruled against renal involvement in human essential hypertension.

The participation of a positive renal factor in chronic hypertension has been recently denied by Grollman (160). He pointed out that in chronic hypertension, the removal of the kidneys was not followed by a reduction in blood pressure. It is equally possible that in chronic hypertension the prolonged action of a humoral agent on the vascular musculature produced an alteration in the metabolism of the muscle cells which was not readily reversible and which persisted after the initiating or sustaining stimulus had been removed.

One of the drawbacks to the acceptance of the renin hypothesis in the etiology of hypertension has been the phenomenon of tachyphylaxis. Page & Taylor (161) have recently found that the previous administration of tetraethylammonium ion overcame this phenomenon and actually augmented the response to angiotonin. These findings introduced a further complication since they raise the question of why a substance, such as angiotonin, whose action is predominantly musculotropic, should be affected to so marked a degree by blockage of the sympathetic ganglia produced by TEA.

Among the substances which have been claimed to be related to the hypertensive syndrome are "1-dopa" [Page & Reed (162)], and tissue aldehydes from the kidney [Øster (163)]. Various pressor substances have been reportedly found in the urine of hypertensive individuals. Lockett (164) described a base in the urine of dogs subjected to renal ischemia which was similar to a base liberated by alkaline hydrolysis of normal urine. No causal relation between the development of hypertension and these substances has been claimed. De la Barreda & Jimenez-Diaz (165) could not differentiate between urine from normal and hypertensive patients. Von Euler & Schmiterlöw (166) found that it was possible to demonstrate a pressor substance with a sympathin-like action in normal blood only by first adsorbing depressor substances with Fuller's earth. Kreuzfeldt (167) could not differentiate between the constrictor effects of plasma and serum from normal and hypertensive patients when perfused through the isolated rabbit ear. Taquini & Fasciolo (168) were unable to demonstrate the presence of renin in the plasma of patients with essential hypertension. More re-

cently, Taquini (169) has reported that the renin titer in the blood of hypertensives was actually lower than that of normal individuals.

Page, Ogden & Anderson (170) found that the blood pressure fell in hypertensive rats after adrenalectomy or hypophysectomy and could be restored by the administration of large amounts of desoxycorticosterone (DCA) or cortical extracts. More recently, Zweifach, Shorr, Baez & Rosenfeld (171) have found that the kidneys of adrenalectomized rats, cats and dogs progressively lost the capacity to produce the vasoexcitor principle (VEM) which appeared in the blood of hypertensive animals. The administration of DCA restored the capacity of the kidney to produce the renal vasoexcitor principle. The question remains as to whether the withdrawal of the adrenal hormones from the circulation produces a specific lesion in the kidney VEM mechanism, or whether the generalized cellular dysfunction, characteristic of adrenal insufficiency, is the factor responsible for the decline in the blood pressure of both normal and hypertensive individuals.

Treatment of hypertension has been attempted by a variety of procedures. Stevens and co-workers (172) treated human hypertension with kidney extracts freed of renin or hypertensinase, and obtained extremely variable results complicated by toxic effects. Wakerlin and co-workers (173) have been able to produce an antihypertensive effect by repeated administrations of kidney extracts containing renin. This treatment, when carried on for several months, was effective not only in reducing the blood pressure of hypertensive dogs but served to prevent the appearance of hypertension in instances where the renal artery was clamped after the injections of the renal extracts had been started. Goldblatt (157) reported similar findings and attributed them to the development of an antirenin factor. Wakerlin, however, has shown that the antihypertensive effect could be obtained with kidney extracts in which the renin has been destroyed by previous heat or chemical fractionation.

Griffiith *et al.* (174) report the successful treatment of selected hypertensive patients with pitressin. It is not clear whether this procedure had an effect similar to that which was obtained by Ohler & Wakerlin (175) following the administration of paredrine, or whether the pitressin effect could be related to a principle which

neutralized the antidiuretic factor (174). Gregory *et al.* (176) believed that it was hazardous to reduce the blood pressure of hypertensive patients abruptly because of the accompanying curtailment of renal circulation and function. Freis & Wilkins (177) found that pentaquine (an antimalarial agent) had a pronounced hypotensive effect which acted primarily by a depression of sympathetic nerve reflexes. The substance was found to be effective in patients with malignant and essential hypertension but severe toxic reactions limited its usefulness. Dick & Schwartz (178) claimed that the Kempner rice diet lowered the blood pressure of dogs with experimental renal hypertension. The results, however, were not extensive enough to permit a clear-cut evaluation. Lindroth (179) found that, by blocking the lumbar sympathetic nerves with alcohol, it was possible to alleviate the hypertensive symptoms for prolonged periods.

Shock

Gregersen & Root (180) have shown that a 30 per cent reduction of blood volume in traumatic shock was invariably fatal, whereas in hemorrhagic shock a 40 to 45 per cent reduction in blood volume was necessary. Wang and associates (181) came to the conclusion that in shock produced by leg trauma, the reduction in circulating blood volume, of itself, was not of sufficient magnitude to explain the high mortality. Overman & Wang (182) subjected dogs to strong, continued stimulation of the central end of the sciatic nerve throughout the bleeding procedure and found that this produced a high mortality in dogs bled only about 30 per cent of their blood volume. They concluded that in traumatic shock afferent nervous stimuli from the damaged limb, by producing excessive vasoconstriction and tissue anoxia, contributed to the development of fatal shock. It should be noted that stimulation of the sciatic nerve produces a highly abnormal situation in which the animals undergo constant muscular tremors, a situation never observed during the shock syndrome. Evidence of this sort is inconclusive since it could be argued equally well that substances such as kallikrein, adenyl derivatives, histamine, etc., have a causative relation to shock because they likewise predisposed the animal to the deleterious effects of hemorrhage.

Seligman, Frank & Fine (183) have shown that a constant feature of the irreversible hemorrhagic shock syndrome was the de-

velopment of liver damage and congestion. They found, in cross-transfusion experiments on dogs, that irreversible shock could be avoided by maintaining an active circulation through the liver. Furthermore, they were able to reverse the syndrome and to bring about recovery by perfusing the liver directly through the splenic vein in animals who had not responded to transfusion and were apparently irreversible. They could not determine the precise factors in the liver which led to this condition. Gibson, Seligman and co-workers (184), by the use of radioactive isotopes, have shown that a "trapping" of blood occurs in the splanchnic region during the latter stages of irreversible hemorrhagic shock. Huber (185) believed that changes in hematocrit and plasma volume during hemorrhagic shock indicated that there was a withdrawal of red cells from the active circulation over and above that which could be ascribed to the reduced blood volume and consequent hemodilution.

Zweifach, Chambers and co-workers (186), by making direct observations on the mesenteric and omental blood vessels throughout the shock syndrome, were able to demonstrate that during the initial stage of shock only compensatory vasoconstrictor phenomena occured. As the shock deepened and a state of irreversibility developed, the peripheral vascular bed became increasingly hypotonic, a condition which led to the diversion and trapping of blood in the capillaries and venules. Further evidence for vascular dysfunction in the splanchnic region has been recently provided (187, 188, 189).

Howarth & Sharpey-Schafer (190) described after hemorrhage in normal humans a sudden reaction during which the heart became slowed and vascular dilatation of the muscles occurred. McMichael (191) concluded from studies on humans that hemorrhage was the major factor in shock. The reduction in venous return, resulting from the oligemia, led to a fall in right atrial pressure, which then set into play compensatory mechanisms such as tachycardia and peripheral vasoconstriction. He attributed the subsequent profound fall in blood pressure to lack of vasoconstriction, especially in the skeletal muscle. The data are concerned more with the initial phases of shock than with the perpetuating factors, which are a consequence of the reduced peripheral circulation to the tissues.

Shorr, Zweifach & Furchgott (154) made a detailed analysis of

the two phases of hemorrhagic shock, originally described by Zweifach, Lee, *et al.* (192) on the basis of changes observed in the splanchnic circulation. They found that the initial compensatory stage was related to the release by the kidney of a vasoexcitor principle (VEM), whose action on the peripheral blood vessels was to enhance the response to vasoconstrictor stimuli. The subsequent development of a decompensatory stage was found to be related to the deterioration of the circulation in the liver and to the release into the blood of a vasodepressor principle (VDM), the action of which was to inhibit or depress the responsiveness of the peripheral blood vessels.

The findings of Phillips and co-workers (64), on renal clearance during experimental shock in anesthetized dogs, indicated an almost complete curtailment of renal blood flow during the development of profound hypotension. Selkurt (193) measured renal blood directly by inserting a cannula into the renal vein and found that these blood-flow measurements did not directly parallel clearances of PAH and creatinine. He suggested that, with prolonged renal ischemia, sufficient tubular damage occurred to impair the extraction of PAH and the reabsorption of creatinine. Mallory (194), in a histological study, found extensive tubular damage to be a consistent feature in kidneys of patients suffering from traumatic shock. Brun, Knudsen & Raaschou (195) observed that following circulatory collapse on a tilt table there developed a persistent oliguria during the postsyncopal period. The effect appeared to be due to antidiuretic factor affecting the reabsorption of water by the renal tubules.

The early and marked development of renal ischemia was found to be paralleled by the appearance in the blood of a renal vasoexcitor substance (151). VEM progressively disappeared from the circulation as a result of the complete curtailment of renal blood flow during the period of profound hypotension. In addition, renal ischemia for prolonged periods resulted in progressive damage to the cellular mechanism responsible for the elaboration of VEM. A complete deterioration of this mechanism was found to have occurred in the kidneys of animals in irreversible hemorrhagic shock after unsuccessful transfusion. This deficiency constitutes a further factor contributing to the inability of such animals to maintain an adequate peripheral circulation.

Selkurt and co-workers (193) believed that the trapping of

blood in the splanchnic region during the latter stage of shock was a consequence of an increased resistance to flow through the liver. It remains to be determined whether the hepatic anoxia, resulting from the reduced circulation through the liver, brings about (as stressed by Shorr, Zweifach and co-workers) the local accumulation of VDM and sufficient vascular dilatation to disrupt the intrahepatic blood flow. This would explain the trapping of blood in the hepatic and splanchnic circulation.

Zweifach and co-workers (186) have stressed the predisposing action of various anesthetic agents on the development of decompensatory circulatory changes during experimental shock. Powers, Reed & Gregersen (196) found that dogs subjected to trauma and hemorrhage under morphine sedation were more susceptible to shock than unanesthetized dogs.

A wide variety of changes in the blood and tissues during shock have been reported, but the precise relationship of these disturbances to the vascular dysfunction characteristic of the syndrome remains uncertain. These are discussed in another section of this volume by Wilhelmi.

Zamecnik, Nathanson & Aub (197, 198) concluded that the development of shock following the injection of clostridia toxins into the dog was the result of vascular damage involving loss of tone and increased capillary permeability. Zweifach and co-workers (186), studying the reactions of the peripheral blood vessels in the omentum and mesentery of cats and dogs, found the administration of clostridia toxins produced in most animals vascular changes characteristic of generalized fluid-loss, and only in a few instances was this followed by the vasodepressor stage characteristic of fatal traumatic shock. Anaerobic infection did not participate in the development of the vasodepressor substances found in blood, liver and skeletal muscles during shock (154).

Until recently, attempts to demonstrate so-called "toxic" principles in the blood of shocked animals have depended in large part upon the blood pressure-lowering effect produced by the injection of large amounts of blood from the shocked animal into normal test animals. Cross-transfusion experiments have also been used for this purpose with negative results. Green and co-workers (199) found no evidence for the presence of a toxic factor following ischemic compression shock in dogs. In the experiments of Chambers, Zweifach, Shorr and co-workers no claim has been made for

a "toxic" factor in the initiation of shock. All the evidence has indicated that deleterious factors originate secondarily as sequelae of disturbances initiated by other factors such as blood loss, neurogenic stimuli, etc. Ashworth & Haist (200) have come to a similar conclusion. The injection of "shock" blood, presumed to contain a toxic principle, into a normal animal presents a situation which is different from that in the shocked donor at the time the blood was removed for testing. In the shocked animal, deleterious substances may have a much more pronounced effect because of the predisposing action of a variety of factors such as the prolonged period of inadequate blood flow to the tissues, the inability of organs such as the liver to detoxify these and other materials, and the exhaustion of factors necessary for the maintenence of vascular tone. Hence, the failure to demonstrate the presence of deleterious substances by cross-transfusion procedures does not rule out the participation of such factors in the shock syndrome.

Prinzmetal and co-workers (201) presented evidence for the presence in burned rats of a toxic factor on the basis of the production of capillary congestion in kidneys perfused with blood from burned animals. McCarthy *et al.* (202) likewise claimed that their transfusion experiments implicated an injurious factor in the blood of burned rats.

Knisley, Eliot & Block (203) emphasized mechanical disturbances of the peripheral circulation resulting from a gelatinous sludge which appeared in the blood following its passage through traumatized tissues. The significance of this type of change in the progression of the shock syndrome is uncertain since irreversible hemorrhagic shock can be produced in heparinized dogs with a minimum or complete absence of such sludge formation.

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METABOLIC ASPECTS OF SHOCK[1]

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The following review deals with the major lines of recent work on a limited sector of the shock problem, and it is not intended to be exhaustive. An account of the history and contemporary basis of the experimental work on shock can be found in an excellent review by Harkins (1). Much of the work done on the physiology of shock during the late war was discussed by Gregersen in an earlier volume of this series (2). Wiggers has furnished a forthright account of the fundamental problems of shock in an earlier review (3), and more recently he has presented a concise summary of the effects of shock on the myocardium (4). The history of metabolic studies on shock, and an account of the work done in the earlier years of the war, was presented by Engel (5) in 1945. A partial summary of later work may be found in a symposium on hemorrhage held in the New York Academy of Sciences late in 1946 (6). An interesting line of experimental attack on problems of survival in organisms has been followed by Negovski and his collaborators (7). It may be noted here that owing to limitations of language and time the author of this review has not examined the Russian literature. An apology is also offered for any other unwitting omissions of pertinent experimental work.

The initial metabolic responses to hemorrhage or trauma which are seen in the stage of impending or developing shock have been compared to the changes seen in animals subjected to a wide variety of stresses (5, 6, 8). The common factor in these circumstances seems to be an increased demand for energy (which may be sustained for some time) during a temporary dimunution of the oxygen supply. The early changes are not extreme, and they are easily reversible. Their duration and magnitude are functions of the general state of the animal (nutritional state as well as extent of the stores of readily available energy) and of the severity of the applied stress. Eventually, after severe hemorrhage or trauma, the initial changes give way to those characteristic of fully developed fatal shock.

The initial metabolic responses to stress may be summarized as

[1] The period covered in this review extends from July, 1944, to July, 1947.

follows (6, 8 to 11). There is a sustained increase in blood glucose, as well as smaller increases in lactate and pyruvate. The ratio of lactate to pyruvate is normal, indicating that mainly oxidative metabolism still predominates in the peripheral tissues. These changes are not seen in the adrenodemedullated animal, and are presumably due to reflex discharge of epinephrine. Plasma ascorbic acid and cholesterol change only slightly, and there is no change in plasma amino nitrogen. In the dog after a nonfatal hemorrhage Kline (17, 18) has found that there is a sustained increase in the output of amino acid from the muscles, and an increase in the uptake of amino acid by the liver. No net change in plasma amino nitrogen occurs. Engel & Engel (8) find that after a nonfatal hemorrhage in the nephrectomized rat there is a prolonged high rate of accumulation of urea in the blood for three hours following the injection or infusion of an amino acid mixture. In control rats the output of urea is equally high only in the first hour after the administration of casein hydrolysate, subsiding rapidly thereafter to the basal rate. The increase in nitrogen catabolism observed in these experiments may be related to the increased nitrogen excretion often seen in patients during recovery from injury. Hepatic function in respect to amino acid assimilation and urea synthesis therefore does not seem to be impaired at this stage. This is supported by the observation of Darrow & Engel (19) that there are no striking changes in the concentrations of liver water and electrolytes, as well as by the observations (20, 21) that the rates of oxygen uptake, deamination and urea synthesis by liver slices, and the concentrations of ammonia, amide, and amino nitrogen in the liver tissue are nearly normal in the rat after a nonfatal hemorrhage.

During this period the liver glycogen tends to fall, and since the blood sugar may remain high for a considerable time, it is probable that there is increased formation of new carbohydrate by the liver from the lactate, pyruvate, and amino acids brought to it in increased amounts from the peripheral tissues. This may be expected in view of the pronounced activation of the adrenal cortex that is observed consistently as one of the earliest responses to stresses of many kinds [Sayers *et al.* (9, 22)]. Following exposure even to quite mild stresses, there is a prompt fall in the concentrations of cholesterol and ascorbic acid in the adrenal cortex. Since the same changes can be brought about by a single injection of adrenocorticotrophic

hormone, it is concluded that they are evidence of increased secretory activity of the gland. Normally, or after a nonfatal stress, the concentrations of cholesterol and ascorbic acid return to or near the "resting" levels in twenty-four hours. The adrenal cortex of the hypophysectomized animal does not exhibit any changes in cholesterol and ascorbic acid concentration in response to stress. It appears, therefore, that in the normal animal one of the primary responses to stress is an increased secretion of adrenocorticotrophic hormone by the anterior lobe of the pituitary gland (brought about, most probably, by epinephrine, but possibly also by reflex nervous activity) and in consequence an increased output of hormones by the adrenal cortex. The importance of increased cortical activity may be appreciated from the fact that both hypophysectomized and adrenalectomized animals are extraordinarily susceptible to stresses of all kinds, but it is not yet possible to describe the actions of the cortical hormones except in the most general terms of their effects on the circulation, on the mobilization and catabolism of protein, and in facilitating the formation of new carbohydrate.

As shock develops, the concentrations of adrenal cholesterol and ascorbic acid fall to lower levels than those reached in the initial response to stress, and they do not return to the normal levels (9). Continued intense stimulation of the adrenal cortex may be such that the demand for cholesterol and ascorbic acid outruns the supply. In the guinea pig, in which the supply of the vitamin might be a limiting factor in the response to severe stress, pretreatment of the animals with large doses of ascorbic acid greatly increases the proportion surviving after a severe, usually fatal hemorrhage (23, 24). It has not yet been shown that the administration of ascorbic acid at a time when shock has fully developed can bring about recovery; further experiments by Dosne de Pasqualini to investigate this point in guinea pigs have not so far been successful (25). Most of the important points bearing upon the role of the adrenal cortex in shock still require illumination (26, 27). The problems have been reviewed in detail by Swingle and associates (26). It is not certain that the activity of the adrenal cortex remains unimpaired in severe shock, and the disappointing results of the administration of large doses of the hormone to animals in shock suggest that the tissues lose their ability to respond to the hormone, or that the functional integrity of the liver may be necessary for the activation of administered hormone. The recent

observations of Roberts & Szego (28) that the liver plays a part in the activation of estrogens, apparently by bringing them into water-soluble combination with a protein, suggests that the liver might play a similar part in the activation of the adrenal steroids.

The metabolic changes characteristic of fully developed shock are in part an exaggeration of the initial changes and in part new, arising in consequence of the diminution in circulating blood volume and of the cutting off of the supply of oxygen and nutrients to the tissues. The blood sugar, which may at first be high, begins to fall, especially in the terminal stages of shock (10, 12, 13, 14, 29, 29a). The fall in blood sugar may be related to depletion of liver glycogen in rats in tourniquet shock [Haist *et al.* (14, 16)]; in rabbits in gravity shock [Nastuk (30)]; in rats in Noble-Collip, tourniquet, and hemorrhagic shock [LePage (31, 32)], and to a marked increase in the utilization of carbohydrate by the peripheral tissues. Russell, Long & Engel (33) have shown that a fatal hemorrhage in the eviscerated functionally hepatectomized rat brings about a greatly increased rate of fall of the blood sugar, indicating rapid utilization of carbohydrate by this "peripheral tissue" preparation. Beatty (13) has also provided evidence of increased sugar utilization by the muscles of dogs in shock after hemorrhage. Additional evidence is provided by the frequent observations of depleted muscle glycogen in animals in shock (16, 30, 31, 32).

Accompanying the increased utilization of carbohydrate, there are increases in blood lactate and pyruvate and a striking rise in the ratio of lactate to pyruvate (10, 12, 13, 33 to 38), indicating a shift toward anaerobic metabolism in the tissues. The contribution of the peripheral tissues to these changes is dramatically illustrated by the nearly vertical trajectory of the blood lactate curve in eviscerated rats after hemorrhage (33) and by the high levels of muscle lactate and pyruvate found in rats in Noble-Collip, tourniquet, or hemorrhagic shock (31, 32). Since for equal energy output anaerobic glycolysis is several times as costly as the oxidation of carbohydrate, the combination of an increased energy demand with anoxia is principally responsible for the increased rate of utilization of carbohydrate in shock.

The outpouring of lactate from the tissues may be correlated with a marked fall in arterial plasma carbon dioxide and in blood pH (38). The acidosis of shock has long been recognized, and many attempts have been made to correct it by providing alkalinizing

agents such as sodium bicarbonate, and more recently, sodium salts of readily oxidizable metabolites, e.g., succinate or lactate. The results of recent experiments (39, 40 to 45) suggest (*a*) that sodium bicarbonate or even sodium chloride in large amounts may be superior to sodium succinate or lactate; (*b*) that survival is often prolonged, but recovery is not critically determined, by correction of the acidosis; (*c*) that succinate, although readily oxidized, may compete too effectively for the limited oxygen supply, depress other more essential oxidative processes, and worsen, rather than improve, the condition of the animal; and (*d*) that the sodium salts of metabolites may be more effective after transfusion, when the improvement in circulation and oxygen supply to the tissues provides a better opportunity for the oxidation of the substrates and the liberation of their associated base.

A large increase in serum inorganic phosphorus after either hemorrhage or trauma has been noted by several groups of workers (30, 34 to 37, 41, 46). Allison *et al.* (46), in a careful study on dogs after hemorrhage or trauma, noted the coincidence of the early increase in plasma inorganic phosphorus with the fall in pH, and found a close correlation between an increase in red cell inorganic phosphorus and the increase in plasma phosphorus. The authors suggest that the depression of renal function in the shocked dogs may be responsible for the observed increases. Other factors may be the breakdown of labile organic phosphorus compounds in muscle and other tissues (31, 32), the depression of liver function, and possibly some alteration in parathyroid activity during shock.

One of the most significant changes in blood chemistry during shock is a rise in blood, or more particularly in plasma amino nitrogen (8 to 11, 17, 21, 33, 35, 36, 37, 47 to 50). In the rat the increase in blood or plasma amino nitrogen after hemorrhage is a rough indicator of the severity of shock (10, 11); it may be correlated with the fall in blood pressure and in portal venous oxygen and carbon dioxide content (49), with the rates of oxygen uptake, deamination, and urea synthesis by surviving liver tissue slices (20, 21), and with the failure of urea synthesis after hemorrhage in the nephrectomized rat (8). The increase is due in part to an increased outflow of amino acids from the muscles (17, 18, 33), in which the concentration of amino acids is significantly increased (48), but mainly it is due to failure of the liver to assimilate amino acids. (It may be noted here that the term "assimilate" applies to

the anabolic metabolism of protein and amino acids as well as to the catabolic reactions of hydrolysis, deamination, and urea synthesis. This point has not always been appreciated in discussions of the role of the liver in nitrogen metabolism in shock or after trauma.) Engel, Harrison & Long (49) have shown that hepatic anoxia due to arrest of the circulation *in vivo* (in an eviscerated rat preparation in which the blood supply to the liver is provided only by the hepatic artery) leads to progressive failure of the liver to remove amino acids from the blood. If the period of anoxia is longer than forty minutes, the liver may add amino acids to the blood for a time after the circulation is restored, and it recovers its ability to assimilate amino acids slowly and only in part during a two-hour period of re-established circulation. This recovery may be associated with the partial recovery of the oxidative metabolism of the liver tissue in the same rat preparation when the circulation is re-established for two hours after a period of anoxia of one to two hours (51, 52). Hoar & Haist (47) and Seligman and co-workers (37) have also observed that the rise in blood amino nitrogen, once established, is only slowly reversed in circumstances in which some of the changes in carbohydrate metabolism can be reversed. The concentration of free amino acid in the liver rises with increasing severity of shock (48, 50) and since there is no accumulation of ammonia the failure of deamination and urea synthesis must go hand in hand (20, 21, 48). These observations may be correlated with those of Grieg and her co-workers (53 to 59) and of Alexander (60) on the destruction during the anoxia of hemorrhagic hypotension in dogs of liver enzymes and coenzymes, in particular, the destruction of cocarboxylase, cozymase, and alloxazine adenine denucleotide and the inactivation of the protein moieties of amino acid oxidase and lactic dehydrogenase.

The carbohydrate metabolism of the liver is also seriously impaired in shock. Haist and co-workers (14, 15, 16) have observed that rats in tourniquet shock fail to store glycogen in both liver and muscles after the administration of glucose by stomach tube, and that insulin is ineffective in bringing about glycogen storage in these circumstances, although the injection of insulin is followed by a considerable fall of the blood sugar from the high levels characteristic of the early stages of tourniquet shock. The absorption of glucose from the gastrointestinal tract appeared to be complete in the shocked rats (although no determinations of absorption rates

were made). Goldberg & Fine (61), measuring rates of absorption of water, isotonic glucose, and saline from intestinal loops of dogs in hermorrhagic shock, find that the absorption rates of water and glucose are diminished as shock becomes more severe. This may be related to the observations of Necheles *et al.* (62) that gastric and upper intestinal mobility diminish with increasing severity of shock after hemorrhage in dogs. The conversion of fructose to glucose, a process which may take place largely in the epithelium of the small intestine, also appeared to occur normally in the shocked rats. The abnormalities of carbohydrate storage in the liver were evident at a time when the muscle, as judged from the levels of phosphocreatine and adenosinestriphosphoric acid, were relatively little affected.

Of the tissues (brain, heart, muscle, kidney, liver) examined by LePage (31, 32) in rats in the terminal stages of Noble-Collip, tourniquet, and hemorrhagic shock, the liver showed the most complete depletion of the stores of adenosine polyphosphate compounds and other sources of readily available energy. Kidney was next most seriously affected; brain, heart muscle, and voluntary muscle had considerable reserves of labile organic phosphate compounds at the time of death. The order of resistance of the tissues to depletion of their stored energy is a function, roughly, of their relative capacities for anaerobic glycolysis, although it is modified by two other factors: (*a*) the size of the stores of phosphate bond energy (greatest in muscle), and (*b*) the degree of restriction of the circulation and the oxygen supply (earliest and most severe in liver and kidney). The first modifying factor is especially attractive to the workers at Wisconsin, who have presented their studies (31, 32, 35, 36) in support of the hypothesis that the essential feature of fatal shock is the critical exhaustion of the supplies of readily available energy, in the form of phosphocreatine and adenosine triphosphoric acid. In their terms (32) "a tissue is assumed to be dead, in the biochemical sense, when the immediately available energy reservoirs—the adenosine polyphosphates—are completely lacking." This thesis derives sensibly from studies on cell-free tissue preparations in which it is often found that the effective operation of complex enzyme systems *in vitro* requires, among other things, the addition or the maintenance of effective concentrations of adenosinetriphosphoric acid (63 to 66). It is a somewhat extreme view, however, even on the author's own evidence, since

the energy reserves of heart and brain, two of the most critical organs, are found to be in relatively good order at the time of death of the animals. In organs like the liver and kidneys, which have relatively low stores of adenosine polyphosphates and a limited glycolytic capacity, the importance of immediately available phosphate bond energy can be readily appreciated. But it is probable that not all biological energy transformations require the mediation of the adenosine polyphosphate system and that in mediating systems of this type the level of the mediator may be very low for quite large energy transfer through it, if production and demand are in balance. This work is interesting and important, since it represents an attempt to apply a rather new biochemical concept, derived largely from studies of cellular metabolism, to an important physiological problem. It is therefore regrettable that the data, representing a coordinated study of blood and tissue chemistry in the rat in shock induced by three different methods, are presented almost entirely in figures so small and complex that an accurate appraisal of quantitative differences between individual values is impossible. This is a most unhappy instance of the combination of the wartime paper shortage and an editorial passion for compression.

The relatively good order of the energy reserves of heart muscle and brain found by LePage (31, 32) indicate that metabolic events in these organs may not be seriously effected until an advanced state of shock has developed. There is good evidence that cardiac activity may be depressed in shock (4) probably owing to the smartly reduced coronary flow during the period of hypotension (67). There is little supporting data on cardiac tissue metabolism in shock. Furchgott & Shorr (68) have reported finding a diminished rate of turnover of high-energy phosphate compounds in heart muscle slices from animals in shock, and Burdette & Wilhelmi (69) have observed less than normal rates of oxygen uptake of heart muscle slices from rats in the terminal stages of prolonged hemorrhagic shock (70). A more careful study, particularly of the changes in heart tissue metabolism during the first period of hypotension, is required. There is also little data on the metabolism of the brain in shock. Rosenthal, Shenkin & Drabkin (71) found no significant changes in the rates of oxidation of glucose and pyruvate in brain tissue suspensions from animals in hemorrhagic shock, in

carbon monoxide poisoning, or after temporary arrest of the circulation to the brain. Wilhelmi *et al.* (72) also found no significant depression of rates of oxygen uptake, in rates of lactic acid formation, and in content of ammonia, amide and amino nitrogen in slices of cerebral cortex from rats in shock both after acute blood loss and after prolonged hemorrhagic shock (70). The present methods of studying tissue respiration may not be adequate to deal with so delicate a tissue, since the routine of handling may so depress the metabolism of the tissue that significant differences between control and experimental samples may be wiped out. The fact, however, that recovery may be brought about by vigorous treatment of animals in late stages of shock suggests that serious changes in brain metabolism may occur only shortly before death or that not the whole brain but one or more of the regulatory centers too small to be accessible for study by present methods is critically affected in the terminal stages of shock.

The general metabolic pattern in advanced shock is consistent with the view that the tissues are subjected to progressive severe anoxia owing to prolonged reduction in blood and oxygen supply. Liver and kidney are affected earlier and more profoundly than the other tissues, which may be protected by the homeostatic mechanisms designed for their defense or which, like muscle with its large capacity for anaerobic metabolism, are better able to withstand the stresses of anoxia and diminished blood supply. One may ask how far the consequent changes in tissue metabolism are critical for the development of "irreversibility" in shock. Haist *et al.* (14, 15, 16) and Meyer, McShan & Goldman (36) have observed that reclamping of the legs of rats in tourniquet shock is followed by reversal of the carbohydrate changes in blood, muscle, and liver seen during shock, but the reversal is not complete if reclamping is too long delayed. Seligman and co-workers (37) have also reported that the changes in blood glucose, pyruvate, and lactate seen in the phase of hemorrhagic hypotension are reversed in the posttransfusion period, and that the animals apparently recover their ability to remove injected glucose, lactate, and pyruvate from the blood, whether they survive or not. In all of these instances the blood amino nitrogen changed little and only slowly. Seligman *et al.* (37) conclude that at least some of the disturbances in metabolism seen in shock are not critical since they may

be reversed without affecting survival. Some more fundamental factor must be responsible for the development of the irreversible state.

One or another of the "toxic factors" that have been proposed from time to time may be concerned. Aub and co-workers, in a series of excellent papers (73 to 81) on experimental traumatic shock in dogs, have shown (*a*) that shock after muscle ischemia may be complicated by the products of bacterial flora, in particular clostridia, which readily grow and produce toxin in ischemic muscle, and which may easily be introduced in the course of traumatizing procedures; and (*b*) that the toxins of *Cl. welchii* and *Cl. oedematiens* (Novy), if injected into dogs in the quantities and at the rates which most nearly simulate the conditions of toxin production by the organisms, can by themselves produce many of the symptoms of shock. Bacterial contamination is not, however, a general phenomenon in shock. Bielschowsky & Green [for literature see Stoner & Green (82)] have advanced the hypothesis that adenosine derivatives, released from injured or anoxic tissues, are responsible for the circulatory collapse in shock. Studies by other workers [Bollman & Flock (83, 84), MacFarlane & Spooner (85)] on breakdown and resynthesis of labile phosphate compounds in ischemic muscle, and the work of Kalckar & Lowry (86), who used an elegant combination of specific enzymatic and spectrophotometric methods to measure adenosine derivatives in the blood of dogs and rabbits in shock, do not support this hypothesis. H. D. Green *et al.* in a paper (87) containing an excellent summary of the literature, reported that, in cross-transfusion experiments with dogs, they found no evidence for a toxic factor in shock, but there is not general agreement on this point (88).

The disturbance in tissue metabolism in shock suggests that substances normally produced by one or more organs might, in the distressed internal environment, escape from regulation and by their unopposed effects contribute to the final collapse of the organism. This is the hypothesis that has been developed from the work of Zweifach *et al.* (89) on the apparent humoral origin of the hyper- and hyporeactive phases of metarteriolar and precapillary behavior in shock, and from that of Shorr, Zweifach & Furchgott (90), who have sought the humoral agents in the affected tissues. Their principal observations are as follows: (*a*) Early in shock the kidneys produce a vasoexcitor material (VEM) that enhances the effects of

epinephrine on the metarterioles and precapillaries of the rat mesoappendix. (*b*) The kidney, *in vivo* and *in vitro*, produces VEM in response to anoxia. The early production of VEM can be related to the shutdown of renal bloodflow observed by Van Slyke *et al.* (6, 91, 92) and Selkurt (93, 94) soon after hemorrhage or trauma, and it may be part of the homeostatic mechanisms designed to restrict the diminished volume of blood to the larger vessels. (*c*) Both kidney and liver can destroy VEM anaerobically, but the capacity of kidney to produce it is lost after prolonged anoxia. As shock and anoxia deepen, therefore, VEM may disappear from the blood. (*d*) Anoxia of liver and muscle, *in vivo* or *in vitro*, results in the production of a vasodepressor substance (VDM) which depresses the reactivity of the minute vessels of the rat mesoappendix to epinephrine. (*e*) Only the liver can destroy VDM oxidatively, and it loses this capacity readily after only moderate anoxia. (*f*) A liver enzyme system has been prepared and partly purified (95) which can inactivate VDM. (*g*) VDM has been prepared in concentrated form, and with this preparation it has been shown (96) that renal excretion may be as important a means of removal of VDM from the blood as its oxidative inactivation by the liver. (*h*) Owing to the restricted peripheral circulation, the liver rather than the muscles provide the chief source of VDM in the late stages of shock. In brief, progressively severe anoxia in shock results in a derangement of normal "hepato-renal circulatory homeostasis." VDM, produced by the anoxic liver, cannot be destroyed or excreted; renal production of VEM fails; it is overwhelmed, blood begins to pool in the minute vessels (possibly chiefly in the splanchnic region), and refractoriness to transfusion develops and is steadily reinforced until death occurs.

The weakest aspect of this work is that the measurements of VEM and VDM are based on observations of altered reactivity of the metarterioles and precapillaries of the rat mesoappendix. They are therefore more subjective and less exact quantitatively than is desirable, and it is to be hoped that more precise methods of estimation can be developed. Meanwhile, the facts are consistent with many other observations. Splanchnic pooling of the blood in late shock has been observed by Wiggers and co-workers (97 to 101) who have noted capillary congestion, passive edema, congestion, and hemorrhage in the intestinal mucosa, development of hepatic resistance to blood flow and persistent high portal pressure, appar-

ent reduction of resistance in the mesenteric vessels, and a shift to the splanchnic region of the major part of the residual blood after bleeding out in dogs in hemorrhagic shock. Gibson *et al.* (102) have also observed a diminution of capillary blood flow in all organs, owing to trapping of red cells and plasma in the minute vessels with a consequent reduction in circulating red cell and plasma volume greater than is accounted for by the external losses of blood. Gregersen and co-workers (103 to 106) have shown that the residual blood volume for 50 per cent survival (RBV_{50}) is greater (73 ml. per kg.) for dogs in traumatic shock than it is for dogs in hemorrhagic shock (59 ml. per kg.), that deafferenting the legs of traumatized dogs leads to reduction of the RBV_{50} (to 65 ml. per kg.), and that stimulation of the central end of the sciatic nerve in dogs after hemorrhage raises the RBV_{50} significantly and may lead to a fatal outcome of an otherwise nonlethal hemorrhage. This work may be related to the observation (96) that the kidney may play an important part in removing VDM and to the observations of Trueta *et al.* (107) that stimulation of the central end of the sciatic nerve leads to diversion of the renal blood flow wholly or partly from the cortex to short-circuits through medullary or subcortical vessels. There is some indication, from work being done in our laboratory of physiology (108) that the renal effects of afferent nerve stimulation can be obtained from any large peripheral nerve, if the time of stimulation is long enough. The afferent nervous factor in traumatic shock may therefore be of great general importance, and it may, of course, be a critical factor in the etiology of the crush syndrome (109, 110).

The importance of the liver in the development of irreversibility in shock is beautifully illustrated by the cross-transfusion experiments of Seligman, Frank & Fine (111, 112). Hemorrhagic shock irreversible to transfusion is induced in dogs by bleeding them out into a Lamson bottle and maintaining a low blood pressure until the animal begins to "take up" blood from the reservoir bottle. The return of all the lost blood at this time fails to bring about recovery. In their first series of experiments, the livers of the bled dogs were perfused through the splenic vein with blood from a donor dog; a return connection is established so that no net exchange of blood takes place. In every instance the animals with an independent hepatic blood supply survived a period of bleeding out that is invariably fatal to control dogs. Cross-transfusion through a

peripheral vein (jugular or femoral) had no effect on survival. The prevention of liver damage during shock, therefore, seemed to assure recovery of the animals. In the second series of experiments, the cross-circulation was not established until "taking-up" of blood was clearly under way. In eight out of nine instances, perfusion of the liver for periods of four to nine hours brought about recovery of the dogs in shock. In these experiments, "taking-up" of blood continued for some time after cross-transfusion was established, and extra blood (averaging 69 ml. per kg.) had to be given to maintain the donor's blood pressure. The "taking-up" diminished and ceased as the condition of the shocked dogs improved. In seven out of nine instances perfusion of shocked dogs through the femoral vein failed to bring about recovery. In this series the blood "taken up" averaged 123 ml. per kg.; this supplementary transfusion was not in itself effective.

These experiments indicate that if enough time is allowed the restoration of an adequate hepatic circulation can bring about repair of the liver to a stage permitting recovery from profound shock. The difficulty of the problem of treatment by less radical means is emphasized by the long period of cross-transfusion required to restore the recipient dogs. The authors are conservative in relating their work to the work of Shorr *et al.* on VDM. It appears that removal of VDM and suppression of its formation cannot be the whole explanation of recovery, since the liver and kidneys of a healthy donor dog must have been equally available for this purpose in the peripheral cross-transfusion experiments. Very likely the restoration of other essential liver functions, many of which may not have been noted or even suggested by the gross metabolic changes summarized in the foregoing pages, is essential to recovery from profound shock.

The studies on metabolism in shock have provided useful experience to students of cellular metabolism as well as to physiologists and clinicians. First, it is gratifying to find that the behavior of enzymes and enzyme systems under changing conditions in the intact organism is not seriously different from their behavior *in vitro*. Second, it is exemplary to learn that the consequences, in physiological or functional terms, of the disturbances of cellular metabolism in one or more organs are not simple and are not easy to interpret or predict. Third, the metabolic studies emphasize the point that an animal or patient who has been in shock and has

survived still faces a considerable problem of repair, but they also define the problem and prepare the ground for improving treatment during recovery and convalescence. Finally, these studies have reinforced and complemented the more extensive work on the dynamics of the circulation in shock, and have provided a basis for the kind of coordinated experimental work which should lead to a unified and comprehensive understanding of the physiology of shock.

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RESPIRATION[1]

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The Control of Respiration

A review of the anatomical and functional organization of the respiratory center has recently been published by Pitts (1). He emphasizes the anatomical distinction of the inspiratory and expiratory centers, and the lack of inherent rhythmicity of the medullary center. According to Pitts, rhythmicity is imposed on the medullary cells by the vagal stretch reflexes and the pontine pneumotaxic center.

The role of pulmonary volume receptors has been investigated by Larrabee & Knowlton (2) in studies on phrenic motoneurones and by Knowlton & Larrabee (3) in single vagus fiber preparations. These workers demonstrated the usual inhibition of phrenic discharge with pulmonary inflation, but found an inspiratory-exciting effect with large inflations. The suggestion that these reflexes are due to activation of two distinct types of receptors is supported by the observation that vagal fibers could be classified into two distinct groups on the basis of rate of adaptation. Slowly adapting receptors are apparently concerned with the inspiratory-inhibiting response important in eupnea, while rapidly adapting receptors are involved in the inspiratory-excitatory reflex probably important only in unusually deep respiration. Rice & Joy (4) found that the respiratory response to central vagal stimulation with shocks of constant potential and wave form varied with the frequency of the stimuli and with the type of anesthetic used. They postulate a central selective action which must be considered in responses to reflex stimulation. Whitteridge & Bulbring (5) conclude that differences in the respiratory effects of various anesthetics are due to specific changes in excitability of the pulmonary stretch receptors.

Breath-holding in forced inspiration produced a reflex drop in

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blood pressure, bradycardia, and a flattening of the T wave in experiments reported by Leimdorfer (6). Breath-holding in expiration had reverse effects. An active respiratory reflex was found by Whitehead & Draper (7) to originate from pressure on the thoracic wall of the anesthetized dog. Smith, Rusk & Masske (8) found increased respiratory amplitude, and often rate, with occulsion of the pulmonary artery in unanesthetized dogs. In anesthetized animals Maaske, Smith & Rusk (9) found respiratory responses to be more variable. Bilateral vagotomy abolished the responses. Conklin (10) reports the changes in respiration induced by tilting rabbits to the head-up position.

Tschirgi (11, 12) points out the importance of both reflex and central mechanisms in gasping of the isolated rat head. Abdominal chemoreceptors play a part in respiratory and particularly circulatory control in the rat and mouse according to Hollinshead (13).

Pi-Suner (14) has reviewed the regulation of respiration by peripheral chemoreceptors. Of particular interest is the author's presentation of data interpreted as evidence of the existence of pulmonary chemoreceptors.

In a pair of interesting reports, Chambers *et al.* (15, 16) discuss the responses and control of respiration in intact and chemoreceptor denervated unanesthetized dogs exposed to anoxia. In the intact dog their findings suggest the presence of a centrally acting stimulating agent supporting the action of the chemoreceptors. In the chemoreceptor-denervated animal they find a well-marked increase in respiratory minute volumes following an initial depression by anoxia. They propose that anoxia produces both depression of central mechanisms and stimulation by some chemical agent, probably not carbon dioxide. These findings support earlier observations of Moyer & Beecher (*American Journal of Physiology*, **136**, 13, 1942) and Gesell's concept of central stimulation by acid metabolites during anoxia. They are also in agreement with the data of Bjurstedt (17). This investigator studied the interaction of centrogenic and chemoreflex control in anoxic chloralose anesthetized dogs by cold-blocking carotid body nerves, concluded that centrogenic drive is markedly decreased during acute anoxia. His records show, however, a tendency for centrogenic drive to increase during the period of chemoreceptor block. With prolonged hypoxia he finds centrogenic drive to become dominant. The results are

interpreted in the light of changes in arterial pH to indicate a parallelism between central drive and arterial H ion concentration. It is also possible that such changes in the arterial buffer capacity may account for the responses reported by Chambers *et al.* (15, 16).

The regulation of respiration in work heavy enough to increase blood lactate concentration was found by Asmussen & Nielsen (18) to depend on a substance, not lactic acid, acting reflexly through the chemoreceptors. Oxygen breathing decreases the production of this substance and depresses its action on the chemoreceptors. Von Euler & Liljestrand (19) question the importance of reflexes in the hyperpnea of moderate muscular work since section of the cord, sympathetics, carotid sinus, and aortic mechanisms did not prevent it. They feel it necessary to return to considerations of direct chemical central action.

Lundin & Strom (20) found the rise in blood lactic acid values during work to have an inverse relationship to the pO_2 of the inspired air.

Frey & Gesell (21) report experiments with difluorophosphate complementing previous observations with carbon dioxide and physostigmine in support of the acid neurohumoral concept of nervous integration. Lillie (22) found similarities in the response of respiratory and hind-limb progression movements to various agents and concludes that common mechanisms operate in both cases.

Krueger & Hunter (23) criticize Gray's Multiple Factor Theory on mathematical and physiological grounds, to which Gray replies (24). It appears to the reviewers that much controversy is avoided when it is recognized, as Gray himself points out, that the Multiple Factor Theory is concerned only with "beginnings and ends of processes and not with intervening steps." It is not, therefore, a theory of respiratory control in the ultimate sense at all, nor do Gray's multiple "stimuli" rule out the possibility of a final common denominator of nervous activity.

The duration of voluntary breath-holding was found by Engel *et al.* (25) to vary directly with inspired pO_2 at barometric pressures less than normal. At higher pressures the effect becomes progressively less. Carbon dioxide plays a related role in influencing breath-holding time under all circumstances (26). These findings are in essential agreement with those of Fenn, Rahn & Otis (27) who found the oxygen factor to be negligible at high oxygen tensions

and the carbon dioxide factor negligible at low oxygen tensions. Mills (28) found that certain subjects regularly showed hyperpnea rather than apnea after forced breathing, a response possibly related to the cortical activity producing the forced breathing.

The Upper Respiratory Tract and Lungs

Mitchinson & Yoffey (29) studied respiratory movements of larynx, hyoid bone, and tongue. Rosin (30) considers the nature of pulmonary tissue grown *in vitro*. Silverman (31) discusses characteristics of the respiratory air flow, and Peterson (32) some applications of aerodynamics to the physiology of the upper respiratory tract. Pressures in the mouth and respiratory passages were measured by Wilhelm, Gilson & Orth (33) under various conditions of spontaneous and controlled breathing. They found no significant differences between oral and "bronchiolar" pressures. Taha (34) made measurements of normal intrapleural pressures among Indians. Maluf (35) produced pleural adhesions in dogs and studied effects on pulmonary expansion and venous pressure. Mack, Grossman & Katz (36) found that artificially produced pulmonary congestion diminished the distensibility of the lung confirming earlier work of Christie. Emmelin (37) reports a bronchoconstrictory action of bile acids. Brookhart & Boyd (38) found a local elevation of intrathoracic pressure in the region of the heart, a finding explained by them on the basis of distortion of the lung.

Dogs subjected to respiratory arrest in an atmosphere of pure oxygen were able to survive for as long as forty-five minutes in the experiments of Roth, Whitehead & Draper (39) and Draper, Whitehead & Spencer (40). This maintenance of life by diffusion respiration occurred in the presence of alveolar carbon dioxide concentrations of about 55 per cent and venous pH of 6.67. Stevens *et al.* (41) showed that oxygen diffuses out of the lungs during breath-holding much more rapidly than carbon dioxide enters.

Riley *et al.* (43) discuss objections to the standard methods of alveolar air collection. They propose instead an indirect method based on determination of arterial pCO_2 and expired air R. Q. Using this concept of physiologically effective alveolar air Lilienthal *et al.* (44) have analyzed the oxygen pressure gradient between alveolar air and arterial blood under a number of conditions of pO_2 and activity. Differentiation of the gradient into two components, membrane resistance and venous admixture is made and

the relative importance of these components discussed. Diffusion constants of the lung calculated by these workers agree well with the values proposed by Marie Krogh.

Drinker & Hardenbergh (45) instilled a variety of protein materials and foreign bodies into the trachea and found only traces to be present in pulmonary lymph and blood.

Blood Gases and Their Transport

The oxygen dissociation curves of fetal and maternal sheep blood were determined by Barron (46). The fetal curves were markedly to the left of the maternal. Synder (47) found that oxygen concentration in the blood of breathing fetuses was considerably higher than commonly believed.

The hemoglobin of Gastrophilus larvae is the subject of observations by Keilin & Wang (48) and Adair, Ogston & Johnston (49). McCutcheon (50) studied the oxygen affinity of hemoglobin in elasmobranchs and turtles. Milam and Muench (51), present hemoglobin levels for specific age and sex groups in North Carolina, Hawkins, Leeson, & McHenry (52), for Canadian population groups. Gibson & Harrison studied relationships between oxygen capacity and iron content (53) and between iron, oxygen capacity and color (54). Hemoglobin values for normal and diabetic dogs are given by Smith (55). Digitoxin seemed to effect an increased utilization of oxygen under conditions of anoxia in the experiments of Benton & Camp (56). Lanphier, Jenny & Pfeiffer (57) studied methemoglobin formation by *p*-aminophenone drugs. Blood carbon monoxide, total hemoglobin, inactive hemoglobin and methemoglobin contents of human blood are considered by Van Slyke *et al.* (58).

Techniques and considerations in the manometric determination of carbonic anhydrase activity are discussed by Roughton & Booth (59). The effects of a variety of factors on activity of the enzyme were noted (60) and discussed with regard to *in vivo* activity. Davenport (61) reviews the role of carbonic anhydrase in tissues other than blood and comments on interpretations of the findings. Day & Franklin (62) comment on plant carbonic anhydrase. Kreps (63) noted variations in carbonic anhydrase activity under such conditions as injections of epinephrine and exposure to low barometric pressure. He proposes that control of enzyme activity, mediated perhaps through the sympathetic system, is

one of the mechanisms of adaption of the organism. The movements and distribution of carbon dioxide and chloride between cells and serum have been studied by Peters *et al.* (64). Penrod & Hegnauer (65) found a drop in arterial oxygen content of pentothal anesthetized dogs apparently due to respiratory depression and hematocrit changes. Behrmann & Hartman (66) studied blood oxygen saturation during pentothal-nitrous oxide-oxygen anesthesia.

Effects of Atmospheric Gases

Oxygen.—The symptoms and characteristics of oxygen poisoning in man have been the subject of observations by Donald (67, 68). In a large group of subjects he found wide variation in tolerance to high pressures of oxygen both as between individuals, and in a given individual from day to day. Pressures as low as 2 atmospheres produced symptoms in two hours. Immersion in water at a given pressure increased the susceptibility to oxygen poisoning.

Stadie & Haugaard (69) found no decrease in the oxygen consumption of mice showing severe symptoms of oxygen poisoning and conclude that hyperoxic anoxia is not the cause of these symptoms. Haugaard (70) demonstrated a relationship between inactivation by oxygen and the presence of sulfhydril groups in enzymes, an observation supported by the work of Dickens (71) who discusses the effect and possible mode of action of high oxygen pressures on a large number of enzymes. The same author (72) reports a thorough study of the toxic effects of oxygen on metabolism of brain tissue. Comparison is made between the mechanism of action of oxygen and that of some of the narcotics. Dickens believes that pyruvate oxidation systems are primarily affected, a conclusion in agreement with that of Mann & Quastel (73). Cass (74) found a partly reversible decrease in carbon dioxide production in frog muscle exposed to high oxygen tensions. Loss of ability to twitch began well before changes in carbon dioxide production.

Dripps & Comroe (75) found a slight but immediate decrease in respiratory minute volume in men breathing 100 per cent oxygen. This decrease, in agreement with the findings of others, changed to an increase as oxygen breathing continued. Bradycardia and reduction in cardiac output also occurred. The rate of increase of arterial oxygen saturation as measured by the oximeter following inspiration of 100 per cent oxygen has been measured by

Fowler & Comroe (76) and the findings discussed. Fasciolo & Chiodi (77) discuss relationships between alveolar and arterial oxygen pressures during inhalation of pure oxygen. They found equilibrium to be definitely incomplete. Christensen, Urry & Cullen (78) determined alveolar and arterial oxygen concentrations during oropharyngeal oxygen therapy. Erythropoiesis was not depressed in guinea pigs exposed to intermittent high oxygen concentrations by Donnel, Jensen & Alt (79). Lindgren (80) recommends high oxygen pressure in cardiac pain and pulmonary edema and Gordh & Norberg (81) studied treatment of cyanide poisoning with oxygen. Hinton (82) injected oxygen into tissues to block the spread of gas gangrene. Smith & Douglas (83) describe prolonged endotracheal oxygen therapy. Oxygen and malaria are the subjects of papers by Ridgon & Rostorfer (84) and Rigdon & Varnadoe (85). Carlson, Lovelace & Burns (86) consider oxygen requirements in aviation and Ferguson (87) comments on the effectiveness of oxygen supply systems. Simpson (88) found little basis for the use of intravenous oxygen therapy.

Carbon dioxide.—The effects of carbon dioxide in concentrations of 7.6 and 10.4 per cent were studied in normal men by Dripps & Comroe (89). Maximal ventilation volumes were lower than those obtained with exhausting exercise or voluntary hyperventilation. A possible narcotic action of carbon dioxide in these concentrations is considered. Banyai (90) considers carbon dioxide as an expectorant in the treatment of cough. Effects of carbon dioxide on the electrocardiogram are described by Altschule & Sulzbach (91) and Durant, Long & Oppenheimer (92). Christensen (93) found that reduction of pCO_2 by hyperventilation could produce ECG. findings compatible with myocardial anoxia. The role of hyperventilation in functional disorders is considered by Carryer (94). Wickwire & Krouse (95) found that excess carbon dioxide prevented insulin-induced hyper-excitability in the goldfish. Mason (96) considers the relation of carbon dioxide to mobilization of body fluids. The assimilation of carbon dioxide in the rat has been studied by Delluva & Wright (97) using carbon isotopes.

Other gases.—Pace *et al.* (98) consider factors affecting rate of uptake of carbon monoxide in man and formulate an equation for estimating the degree of blood saturation with the gas. Goldman (99) suggests an equation for estimating the rate of uptake of carbon monoxide under conditions of varying gas concentration

and respiratory minute volume. Data on denitrogenation in dogs are presented by Karel & Weston (100) and nitrogen elimination in man is discussed by Stevens *et al.* (101). Lawrence *et al.* (102) report preliminary observations on narcotic effects of xenon. Jandorf & Bodansky (103) report on methemoglobinemia in relation to poisoning by hydrogen cyanide. The absorption rates of oxygen, carbon dioxide and nitrogen from the human colon were determined by Pogrund & Steggerda (104).

Resuscitation

Grodins, Lein & Adler (105) followed acid-base changes in the blood of dogs during asphyxia. Their results indicate arterial carbon dioxide and hydrogen ion levels above normal during the entire course of the asphyxia and subsequent artificial ventilation with air. The use of carbon dioxide in resuscitative mixtures is therefore strongly questioned.

Thorp (106) studied the ability of various analeptics to restart respiration in guinea pigs made apneic with barbiturates and Snapp, Ivy & Adler (107) found that commonly used respiratory stimulants only infrequently caused spontaneous resumption of respiration in dogs made apneic by anoxia. De Arellano (108) found that metrazol increased the excitability of the barbital depressed respiratory center, apparently due to a pharmacological antagonism to barbiturates.

The importance of measures aimed at maintenance or reestablishment of circulation seems obvious. Bailey (109) points out the importance of cardiac massage and mechanical stimulation of the ventricle. Reicher (110) feels that suck and blow ventilation combined with cardiac massage is the method of choice. Thompson, Quimby & Smith (111) and Thompson & Rockey (112) find that mechanical inflation and deflation of the lungs produces movement of the blood after cessation of heart beat. They also prefer suck-and-blow respirators and point out the importance of heparin to prevent post-mortem clotting. Beecher (113) discusses principles of resuscitation and anesthesia.

The Pneumatic Balance Respirator (PBR) was found by Motley *et al.* (114) to be a physiologically sound and effective means of providing artificial ventilation. Avoidance of mask leaks was the most difficult clinical problem. Orth, Davis & Moir (115) heartily concur in the recommendation of this simple and compact appara-

tus. Spiro, Aaron & Thompson (116) studied the efficiency of the Eve method of artificial ventilation under various conditions. Reed (117) proposed a modification of the official Red Cross method of manual resuscitation. A seesaw resuscitator for the treatment of asphyxia in the newborn is described by Miller & Davier (118).

Pressure Breathing

Barach *et al.* (119) review the physiology of pressure breathing of the continuous and intermittent types. Barach and his group (120, 121, 122) have reported their observations on pressure breathing with a continuous pressure of 15 mm. Hg. Observations on respiration, circulation, blood gases, and psychological effects under conditions of normal and reduced barometric pressures are reported.

Pressure breathing was found by Bateman & Sheard (123) to produce an initial fall in extremity skin temperature followed by a slow rise which was absent when conscious respiratory effort was abolished. Molomut & Allen (124) found that the cardiac output did not vary from normal during pressure breathing at a simulated altitude of 46,000 ft. although stroke volumes were reduced. Ivy, Snapp & Adler (125) found no increase in intracranial pressure during pressure breathing although respiratory fluctuations were exaggerated.

In man, Dern & Fenn (126) report that increased intrapulmonary pressures raise both systolic and diastolic pressures. Observations were also made on auricular and venous pressures of cats under conditions of varying posture and intrapulmonary pressures. Motley, Werko & Cournand (127) found that cardiac output changes during pressure breathing are related to the type of pressure curve produced by the apparatus used. An analysis of these results in terms of net filling pressures of the heart has been made by Cournand, Motley & Werko (128).

Sheard (129) points out the value of pressure breathing at altitude in maintaining the threshold levels of the retinal rods and cones. Totum & Ginzler (130) found microscopic evidence of emphysema in dogs subjected to intratracheal pressures of 50 mm. Hg. Gross emphysema and carotid air emboli appeared at pressures of 80 to 110 mm. Hg. maintained for periods of 10 sec. duration. Shrader & Kaliss (131) discuss pressurized oxygen therapy and Paton &

Sand (132) consider effects of immersion on pulmonary events at various levels of intrapulmonary pressure.

Clinical Applications

The respiratory activity of the fetus has been studied by Davis & Potter (133). Using roentgenographic techniques these workers present evidence that the pattern of intrauterine respiration is essentially the same as post-partum respiration. Free circulation of amniotic fluid through the fetal lungs was found. Gottschalk (134) recorded respiration in infants during the first hour of life. He evaluates the effect of drugs used during labor and proposes normal values for respiration at this early age. Gruenwald (135) suggests that atelectasis is the normal condition of the fetal lung and that aeration but not aspiration of fluid is resisted due to surface tension. Salmon, Forbes & Davenport (136) discuss airblock in the newborn infant.

Heyer (137) studied the respiratory patterns of patients with cardiac dyspnea and found evidence of reflex bronchospasm. Similar conclusions are reached by Plotz (138) in studies of cardiac asthma. Burch (139, 140) studied the rates of respiratory water and heat loss in cardiacs under subtropical conditions of temperature and humidity.

The classic theory of left heart failure in pulmonary edema is attacked by Wassermann & Goodman (141) who feel that dysfunction of the sinoaortic mechanism is the basis for the condition. Groedel & Miller (142) recorded the intratracheal pneumocardiogram in man. Weintraub & Bishop (143) and Mannheimer (144) discuss cardiac tests based on anoxia.

Respiratory patterns in pulmonary tuberculosis were found by Rao & Silverman (145) to resemble those in asthma in some cases. There was also an abnormal response to increased resistance in the breathing circuit. Birath (146) found evidence of definite impairment of pulmonary function following therapeutic pneumothorax and suggests caution in the use of this therapy. Barach (147) discusses immobilization of the lungs by the equalizing pressure chamber.

Elam, Hemingway & Visscher (148) point out that pulmonary dysfunction may be primarily alveolar or ventilatory in type. The rationale of artificial ventilation and oxygen therapy are discussed in the light of this classification. Barach & Barthwaite (149) dis-

cuss the physiology and therapy of emphysema. The supine horizontal position is best tolerated by anesthetized patients, and Slocum, Hoeflich & Allen (150) consider circulatory and respiratory responses to variation from it. Brody (151) considers prevention of respiratory embarrassment in therapeutic curarized convulsions.

Bain, Sloan & Brucer (152) found evidence of penetration of nebulized substances in the respiratory tree to the level of the large bronchioles. Lowell & Schiller (153) exposed asthmatics to aerosolized pollen extracts and found reduction in vital capacity. Mauer (154) considers tissue anoxia as the cause of clubbing of the fingers. The intravenous administration of a number of gaseous anesthetics was investigated by Jacoby, Livingstone & Geiling (155). Respiration in the anesthetized human is considered by McCann (156).

Miscellaneous

The role of respiration in the control of body temperatures of rats and rabbits subjected to hypothermia has been studied by Ware, Hill & Schultz (157). Mason & Haterius (158) noted respiratory and circulatory changes in fatal hypothemia in dogs. The respiratory excretion of methyl alcohol by rats was investigated by Shea & Hine (159). Karpovich (160) found that breath-holding time was a poor test of physical endurance. Ray, Johnson & Ray (161) believe that the reduction time of blood after breath-holding is related to physiologic fitness and indicates adjustment to conditions of stress. Berg (162) followed the respiratory gas exchange during recovery from moderate exercise. His observations suggest that limiting factors in the rate of oxygen consumption and carbon dioxide elimination are primarily circulatory in nature. Penrod (163) discusses the ventilation of sealed aircraft cabins and Whittingham (164) reviews progress in aviation medicine.

Methods and Apparatus

Kent (165) describes a plastic, expendable oxygen mask, Duncan (166) a helmet for breathing oxygen or other gases and Bech & Dunham (167) an improvised oxygen tent. Chapanis (168) describes charts for demonstrating effects of anoxia on vision. An electronic warning device for oxygen breathing systems has been developed by Tobias & Siri (169). Silver (170) discusses design and operation of gassing chambers.

Methods for determination of the gas contents of small samples of blood or the analysis of small volumes of gas are described by Flagg (171), Flemister (172), Berg (173), Schmidt-Nielsen (174), Scholander (175, 176) and Scholander, Flemister & Irving (177). A method for the measurement of alveolar pressure is described by Otis, Proctor & Rahn (42) and estimates of the work of breathing may be calculated from data so obtained.

Irving, Scholander & Hebel (178) describe apparatus for complete recording of respiratory exchange in man. Christensen (179) for studies on small laboratory animals, Anfinsen & Claff (180) suggest extension of the Cartesian Diver microrespirometer technique, and Robbie & Leinfelder (181) a method for measurement of respiration in aquatic animals. An improved oxygen absorption bulb is proposed by Goodman & Gustavson (182).

Ramsay (183) describes and discusses apparatus for the equilibration of blood and gas mixtures. Courtice & Douglas (184) consider the ferricyanide method of blood gas analysis. Ruhe (185) reports preparation of crystallized oxyhemoglobin.

A spectrophotometric method for hemoglobin determination is proposed by Cohen & Barnard (186) and Baumberger (187) discusses a polarographic analysis of reduction of oxygen by hemoglobin compounds in acid. Hill (188) and Tobias & Holmes (189) comment on the uses of the oxygen electrode.

Anoxia

D'Angelo (190) studied the respiratory metabolism of subjects exposed to mild anoxia (simulated altitudes of 8,000 and 10,000 feet). He found increased respiratory minute volume and changes indicating a respiratory alkalosis. Individual tolerance to anoxia was best correlated with elevation of the R. Q. His results emphasize the importance of considering anoxic effects even at altitudes as low as 8,000 feet when exposure is prolonged. Smith, Seitz & Clark (191), measuring variations in the angioscotoma, also found definite evidence of an anoxic effect during seven and one-half hour exposures to 10,000 feet altitude. Green (192), used a battery of tests on anoxic subjects and concluded that over-all performance during anoxia correlated poorly with the results of any one particular test. Muido (193), found appreciable deterioration of eye-hand coordination at pressure altitudes of 6,000 meters and above.

White (194) found little evidence of deleterious effects in sub-

jects flying for one hundred twenty hours at altitudes of 9,000 to 14,000 feet. Riesen, Tahmisian & Mackenzie (195) found that administration of glucose in water thirty to fifty minutes prior to ascent to 27,,000 and 30,000 feet significantly increased the duration of consciousness at these altitudes. Proger & Dekaneas (196, 197) report amelioration of the effects of anoxia in men and experimental animals as the result of injections of cytochrome-*c*, findings not confirmed by the experiments of Scheinberg & Michel (198).

Pace *et al.* (199) induced artificial polycythemia in men by transfusion of suspended red cells and found increased tolerance to anoxia as measured by pulse rate changes during exercise under conditions of low oxygen tension. They feel that the development of polycythemia is an important feature of acclimatization. Goodman (200) found that when cobalt injections are combined with chronic exposure to anoxia there is no additive effect on the development of polycythemia.

Changes during acclimatization to simulated high altitudes have been the subjects of reports by Houston (201) and Houston & Riley (202). These workers and their colleagues at the Naval School of Aviation Medicine and Research studied the responses of four healthy subjects to a month's exposure to gradually lowered barometric pressure under the controlled conditions of the decompression chamber and laboratory. Their findings essentially confirm the concepts derived from data obtained on high-altitude expeditions under less favorable conditions. Increased pulmonary ventilation and the shape of the hemoglobin dissociation curve, acting to reduce the gradient between inspired pO_2 and mean capillary pO_2 seem to be the most important factors in acclimatization. There was no evidence of change in cellular metabolism as reflected by total oxygen consumption. Houston (203) presents a group of charts showing the integration of various factors in the process of acclimatization to oxygen lack. Rotta (204) examined the cardiac size of natives living at an altitude of 4,540 meters. He found that the cardiac hypertrophy commonly found was frequently associated with clear evidence of predominance of the right heart, attributable to the functional and anatomic alterations of the lungs.

Relations between pulmonary ventilation and the maintenance of adequate alveolar pO_2 in anoxia have been pointed out by

Houston (205) in humans and Stacy & Whitehorn (206) in experimental animals. The latter authors found that the tolerance of the dog to anoxia as compared with the cat was due primarily to a quantitively greater respiratory response to chemoreceptor stimulation.

Using the oximeter, Henson *et al.* (207) collected valuable data on arterial oxygen saturations of subjects breathing air or oxygen at various altitudes. Fenn, Rahn & Otis (208) have contributed a graphic mathematical treatment of the relationships of the alveolar gases, ventilation rates and R. Q.'s at various altitudes. Questions relating to equivalent altitudes, use of carbon dioxide mixtures at altitude and other aspects of high altitude physiology are discussed in the light of the equations presented.

The effect of anoxia on the fertility of male rabbits has been studied by Walton & Uruski (209). Similar studies on guinea pigs are reported by Shettles (210). Stickney (211) found the loss of body weight in anoxic rats to be proportional to the altitude up to 28,000 feet. Lawless & Van Liere (212) were unable to draw definite conclusions from experiments on the water content of various tissues of rats exposed to low barometric pressures. All animals showed significant body weight losses, but tissue water losses were inconsistent. Mild anoxia produces polyuria, and severe anoxia oliguria in anesthetized dogs according to Stickney, Northup & Van Liere (213). In unanesthetized animals, however, oliguria does not occur. MacLachlan (214) found an initial acceleration of gastric emptying time in rats fed corn oil and made anoxic. Van Middlesworth (215) demonstrated an "anoxic diabetes" in rats following severe anoxia. Van Liere *et al.* (216) found no significant effect on the absorption of magnesium sulfate as the result of anoxia.

Harris & Matlock found a diminution in the refractory period of cardiac muscle (217). Conduction rate increased and threshold decreased with mild anoxia, but slowed conduction and markedly increased threshold accompanied severe anoxia (218). Peripheral nerves showed an inverse realtionship between oxygen uptake rates and survival times without oxygen in the experiments of Wright (219). The product of survival time and oxygen uptake rate was a constant for the species investigated. Trowell (220) describes watery vacuolation of the liver as a result of severe anoxia.

Kline (221) found that mixtures of carbon dioxide and oxygen were equal to or better than oxygen in maintaining cats at simulated altitudes up to 43,000 feet, and in restoring animals depressed by anoxia.

King & Henson (222) studied electrocardiographic changes in fulminating anoxia. Finesinger *et al.* (223) found a shift to the slow frequencies of the electroencephalogram and a decrease in verbal and gestural activity in most subjects exposed to low oxygen.

Pitts & Pace (224) studied the effects of various levels of blood carboxyhemoglobin on response to exercise during anoxia. They estimate that a one per cent increase in blood carboxyhemoglobin is equal to an increase in altitude of 335 feet for the altitude range 7,000 to 10,000 feet, and for increases in blood carboxyhemoglobin of at least 13 per cent. Using the visual threshold as a criterion Halperin *et al.* (225) found that increases in carboxyhemoglobin produce effects equal to those produced by reduction in oxyhemoglobin as the result of anoxia. Bodansky & Hendley (226) studied the effects of induced methemoglobinemia during anoxia and exercise.

Grenell & Kabat (227) found no correlation between vascularity and resistance to circulatory arrest in hypothalamic nuclei. Titrud & Haymaker (228) report two fatal and one nonfatal case of cerebral anoxia due to exposure to high altitudes. Effects of low oxygen tensions on sicklemia and sickle-cell anemia were observed by Henderson & Thornell (229). These workers found no greater incidence of exacerbation of the sickle-cell state by exposure to low oxygen pressures. Grant & Root (230) question the belief that low bone marrow pO_2 is the stimulus for erythropoiesis following hemorrhage. Rigdon (231) considers anoxia to be an important factor in the pathology of malaria. The survival of the gasping mechanism in decapitated mice was found by Thoms & Hiestand (232) to be inversely related to age, disappearing at about nineteen days of age. Robbie (233) studied respiratory responses and oxygen consumption of rats poisoned with cyanide and Ward (234) investigated time of appearance of signs of cyanide poisoning in terms of rate of injection. Sullivan (235) discusses anoxia neonatorum, Clement (236) considers anoxia in anesthesia, and Maegraith & Havard (237) comment on anoxia and renal function.

Seabra (238) remarks on changes in oxidase content of red and white blood cells with anoxia.

Effects of Changes in Barometric Pressure

Allen (239) found that normal subjects were able to tolerate explosive compressions at rates as high as 8 pounds per square inch per second and ranges as great as 514 mm. Hg. Bean (240) found a decrease of arterial pH during compression and an increase during rapid decompression. These changes seem best explained on the basis of interference with removal of alveolar carbon dioxide by compressional inflow, and excessive loss of carbon dioxide due to decompressional outflow. They should be considered in explanations of responses to changes in barometric pressure. The well-known concept that changes in "weather" may induce pain in certain disease states has been critically approached by Jones & Schiller (241). They found a correlation between exposure to simulated low altitudes and incidence of joint pain in subjects with symptomatic joint disease. The effect is unexplained. Fegler & Banister (242) studied the congestive pulmonary atalectasis found in animals subjected to low barometric pressures. They found no relationship to pO_2, nor did decompressions from several atmospheres produce the effect. They conclude that absolute rarefaction of air is the prime factor, in the etiology of this condition, although the mechanism involved seems rather obscure.

Berg & Cook (243) found a reduction of carbon dioxide production in humans at pressure altitudes of 30,000 feet, a finding considered by them to support the concept of a specific effect of low atmospheric pressure on metabolism. Since their subjects breathed pure oxygen during the control period at ground level it seems possible that values for carbon dioxide production so obtained were relatively high (unpublished experiments of Hitchcock *et al.*) and the change found at altitude may simply reflect the reduction of pO_2 to more normal levels.

Explosive decompression.—The observations of the Ohio State University group on effects of explosive decompression to simulated altitudes as high as 50,000 feet have been published in a series of papers. Laboratory animals tolerate such decompression well, but anesthetized dogs show a transient hypotension and bradycardia apparently due primarily to increased intrathoracic

pressure and pulmonary distention [Whitehorn, Lein & Edelmann (244)]. Cerebrospinal fluid pressures showed a short-lasting rise which gave no evidence of bubble formation and is considered, again, to reflect intrathoracic pressure changes [Whitehorn *et al.* (245)]. The hemorrhagic lesions in lungs, hearts, and brains of explosively decompressed dogs are discussed by Edelmann *et al.* (246). The sudden increase in intrapulmonary pressure, transmitted to other tissues of the body is considered to be the primary etiologic agent. The concept that the pulmonary damage is due to actual bruising of alveolar tissue by the positive pressure wave, rather than to overdistention and tearing, is supported by experiments of Whitehorn, Lein & Hitchcock (247), who were unable to prevent such lesions by supportive binding of abdomen and thorax in dogs.

These observations have been extended to explosive decompressions to final pressures below the vapor pressure of body fluids, where boiling of such fluids might be expected. Hitchcock & Edelmann (248) describe the sequence of events in dogs decompressed to 30 mm. Hg. Changes explainable on the basis of anoxia were observed, and marked subcutaneous swelling, probably the result of vaporization of body fluids was regularly seen. Decompressions to 30 mm. Hg. repeated daily for five days produced evidence of pulmonary atelectasis in experiments on rats by Edelmann & Stacy (249).

Corey (250) found rats and cats to be highly tolerant of explosive decompression to 35,000 feet or to final altitudes as high as 80,000 feet if immediate recompression was carried out. Animals decompressed to altitudes above 35,000 feet and not immediately recompressed showed a fatality rate of some 50 per cent. Pathology was limited to pulmonary and gastro-intestinal tracts. The observation that restriction of pulmonary expansion by a strap around the upper thorax prevented fatalities following explosive decompression is at some variance with the observations of Whitehorn, Lein & Hitchcock (247) mentioned above.

The cause of death in rats explosively decompressed to altitudes ranging up to 75,000 feet is considered by Gelfan, Nims & Livingston (251) to be anoxic anoxia, since survival times were independent of final altitudes above 52,000 feet where, theoretically, anoxia should be complete since probable alveolar pCO_2 and

pH_2O equal the total barometric pressure. Livingston, Gelfan & Nims (252) found frequent cochlear hemorrhages and marked pulmonary injury in such rats. Their findings suggest a nearly complete arrest of blood flow in the pulmonary circulation, an event of great importance in the consideration of the physiologic consequences of exposure to such extreme altitudes.

Decompression sickness.—The problem of decompression sickness has been the subject of much study. The symptomatology of altitude decompression sickness, the well known effects of altitude and exercise in increasing its incidence and severity, the preventive effects of denitrogenation, and the reliability of selection procedures to determine resistance have been discussed in a series of papers by Gray and his collaborators of the Randolph Field group (253 to 256). Burkhardt *et al.* (257) agree that age, altitudes and exercise are the most important factors predisposing to bends at altitude and that denitrogenation is the most effective method of prevention. A high protein diet predisposed to bends while a high carbohydrate diet had the opposite effect. The validity of selection procedures in preventing altitude pain and the application of results obtained with a given test procedure to other conditions of altitude and exercise are considered by Henry (258). Cheetham (259) questions the validity of selection tests conducted in a chamber with a ground level altitude of 4,700 feet.

Whitten (260) describes scotoma as a complication of decompression sickness, and Houston (261) points out that bends and visual symptoms may appear at altitudes of less than 20,000 feet. While the symptoms of decompression sickness have been well established both for decompression from atmospheric pressures and from pressures greater than atmospheric the exact etiologic mechanisms are not entirely clear in the case of the former. The importance of supersaturation of body tissues with nitrogen is borne out by the many reports of the beneficial effects of denitrogenation and is further supported by the observations of Stevens, Ryder & Ferris (262) who found a correlation between rates of nitrogen elimination and susceptibility to decompression sickness. Whether the offending bubbles are located intra- or extra-vascularly, however, remains controversial. On the basis of x-ray studies Burkhardt *et. al.* (263) felt that the pain of decompression sickness was due to the chance location of extravascular bubbles in relation to

nerves or nerve endings. Gersh (264) concluded that the demonstration of small extravascular bubbles by x-ray is uncertain, at least in the guinea pig. Gersh & Catchpole (265) continue their previous studies and point out that bubbles found in rabbits dying at altitude are always intravascular. The significance of these observations, in the reviewer's opinion, would be considerably enhanced if they had been made on living animals rather than those which had died at altitude. Post-mortem bubble formation was certainly not ruled out.

McElroy & Whiteley (266) contribute further data on the pressure differences necessary to produce intravascular bubbles in pressurized cats decompressed to various final pressures. Effect of mechanical disturbance on bubble formation in cells and tissues decompressed from high pressures of nitrogen have been described by Harvey *et al.* (267). Hodes & Larrabee (268) found that low alveolar carbon dioxide prior to ascent was associated with increased tolerance to decompression sickness in most subjects. Williams *et al.* (269) found no appreciable effects of a number of drugs on decompression sickness. Behnke (270) summarizes recent developments and concepts with regard to problems of high altitude flight. Finally, Tobias, Loomis & Lawrence (271) present significant observations on circulatory changes associated with decompression sickness. These findings indicate that circulatory changes precede the onset of bends pain. Taken with scattered reports of a similar nature from other laboratories they point strongly to the need for further investigations along these lines in the search for a complete understanding of decompression sickness.

An interesting theory as to the cause of pain in aerodontalgia has been advanced by Reynolds *et al.* (272). From a consideration of data collected during indoctrinations in low pressure chambers, these authors conclude that this pain is referred from the maxillary sinus and usually occurs in a tooth which has previously experienced painful stimulation. Experimental evidence in support of this theory is presented by Hutchins & Reynolds (273) in a later paper. Schuessler (274) states that the theory that the expansion of air trapped under fillings is the cause of aerodontalgia is untenable. He considers the possibility of referred pain from the maxillary sinus, but believes that changes in the pulp are a more likely cause of the dental pain.

Atmospheric blast.—Blast injury is discussed by Draeger, Barr & Sager (275). Cohen & Biskind (276) discuss pathologic aspects of such injuries and Miller (277) reports rupture of the heart as the result of blast. Horvath & Shelley (278) found air blast to be relatively ineffective in neutralizing personnel and Shelley & Horvath (279) report that blast effects in closed spaces exceed those in the open.

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ANOXIA IN AVIATION[1]

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Much of the war work on problems of anoxic-anoxia and the relations of these problems to aviation has already been summarized (1, 2), and now there seems to be a declining interest among investigators in this field. This is unfortunate since many questions of both practical and theoretical value remain unanswered. There is need for the development of inexpensive, light weight, expendable oxygen masks and effort must be made to educate civilian flight crews and passengers and make them aware of the hazards of anoxia (3). The anoxic margins of safety in the older pilot especially need to be determined (4). Although much is already known about the anoxic tolerance of the physically fit military aviator (5), precise studies on the younger individual, the adult in the older age groups, or those suffering from various degrees of pathologic abnormality have yet to be done. Such questions are of obvious importance to civilian aviation, since the average altitude of commercial flight is going higher, often without adequate oxygen equipment aboard and with little understanding, among those who are flying, of the oxygen problems involved. Our military airplanes are reaching for altitudes above 50,000 feet, altitudes that raise special problems as to the safety of pilot and crew (6). Special emergency equipment must be developed for man to return safely from these altitudes in case of airplane failure. Death, at altitudes above 52,000 feet, can occur in less than twenty seconds, even if pure oxygen at ambient pressure is supplied (7, 8).

Effects of anoxia.—The arterial oxygen saturation at altitude has been carefully redetermined with the Millikan Oximeter and the measured saturation of 85 per cent at 10,000 feet breathing air or 87 per cent at 40,000 feet breathing oxygen indicate these to be the highest "safe" altitudes in unpressurized airplanes (9). These altitudes should be adhered to for all civilian flight, despite the difficulty of demonstrating, with any single test, deficiencies in

[1] This review covers the period from July 1, 1946 to June 30, 1947.

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either motor or mental function. Testing procedures will have to be much improved. For example, when a battery of five tests were used to determine the decrement in function at 17,000 feet (10), the decrement varied from 26 per cent to −8 per cent in individual subjects on a particular test, and there was poor correlation between tests. On one or more of the tests, each subject showed evidence of a marked degree of impairment. It is obvious that anoxia affects many functions and that these are not affected in the same degree from one individual to another. At 6,000 meters, a considerable deterioration in hand-eye coordination of three subjects was found (11).

Pulse rate has been found to be much more sensitive to anoxia than respiratory rate in human subjects (12), the respiratory rate being relatively insensitive. Pulse rate responses are definite at 93 per cent saturation, showing a progressive increase following a decrease in the amount of oxygen in the blood of the test subjects. Using pulse rate for the most part as an indicator of the functional degree of anoxia, Pitts *et al.* found that 1 per cent increase in blood carbon monoxide is equivalent to a 335-foot increase in altitude (13). Dogs appear to tolerate anoxia much better than human subjects because of greater sensitivity and a more rapid readjustment to the lowered oxygen partial pressure (14). If dogs with chronically denervated aortic and carotid chemoreceptors are exposed to anoxia, there is first a respiratory depression followed by strong respiratory stimulation (15). It appears that the respiratory center in the dog can, after a short period of anoxic depression, be the seat of strong respiratory stimulation which long outlasts the depression. These results are to be contrasted with those obtained by Bjurstedt (16), who believes that anoxic stimulation is entirely caused by chemoreflexes.

A study of the breath-holding ability of human subjects at various altitudes (17, 18, 19) has revealed a linear relation between the duration of the "breath-hold" and the oxygen partial pressure. These experiments have a double interest. They could provide the basis for a convincing method of demonstration to the individual subject that a lack of oxygen is affecting him. They also indicate that an oxygen stimulus to respiration is present in man even at normal oxygen pressures, since, when the partial pressure of oxygen is increased above normal, the ability to hold the breath increases.

In rats, lack of oxygen decreases the ability to perform muscu-

lar work (20). Further study is necessary to understand how this loss of work ability is brought about. Exposure of rats to altitudes of approximately 8,000 to 28,000 feet, causes weight loss in proportion to the altitude (21). A large part of this weight loss must be water lost from the extracellular spaces, since there is little evidence of water loss from the intracellular spaces even after three and one half hours at altitude (22).

The effect of fulminating anoxia on the electrocardiograph of humans and dogs has also been restudied (23). In man, a consistent decrease in the T-wave was the main effect observed. In dogs, the effects were more severe. The T-wave was decreased and inverted initially, but in the final stages, the T-wave was augmented and upright.

The electroencephalograms of subjects exposed to altitudes of 15,000 feet demonstrate that the frequency of the alpha rhythm depends on the oxygen partial pressure (24). The degree of slowing is of statistical significance at 15,000 feet. This "brain wave" change, though not understood, must be the first sign of a process which at higher altitudes leads to severe and irreversible changes. In a histological examination of the brains of two men who died fifty hours and three weeks after accidental anoxic episodes of short but undetermined duration at 20,000 and 24,000 feet, necrosis was observed in many sites of the central nervous system, including regions as far apart as the ganglion cells of the cerebral cortex to anterior horns of the spinal cord (25). This study reemphasizes the narrow margin that exists between reversible anoxic change in the central nervous system and irreversible destruction of parts of this system. What are the factors that determine the sensitivity of regions of the central nervous system to anoxia?

A six-day flight, in which altitudes of 8,000 to 10,000 feet were reached daily, resulted in nothing more than headache and mild fatigue in some of the passengers. These effects disappeared with adequate rest (26). Though the effects reported are mild, it is pertinent to note that such effects could be ameliorated with oxygen equipment. If civilian passengers are to be kept comfortable, they must be provided with adequate oxygen.

The most sensitive system of the body to the effects of anoxia is the visual system, particularly the function of brightness discrimination. The higher the altitude, the greater the impairment of this function (27). It also appears that visual intensity discrimination

at low levels of illumination is as sensitive to anoxic-anoxia as it is to anemic-anoxia, caused for example by the presence of carbon monoxide in the blood (28). However, concentrations of methemoglobin in blood up to 30 per cent seem to be without affect on rod threshold, a result that is somewhat difficult to understand in view of the above (29). At 10,000 feet, there is a progressive and significant loss of visual efficiency due to an increase in the size of the angioscotoma amounting to about 25 per cent after seven and one half hours of exposure (30). The changes in vision are of sufficient magnitude, at the slightly higher altitudes of 15,000 to 16,000 feet, to convince 90 per cent of the indoctrinees of a deterioration in contrast visual sensitivity when simple demonstration charts are employed (31). Such charts should be of great value in high altitude flight training programs.

A recent report states that a substance called "oxidase" leaves the neutrophils and enters the erythrocytes, when rats and other animals are exposed to anoxia (32). The nature and function of this substance is not clearly indicated. For other discussion of the effects of anoxia, see the review by Hitchcock (33) in this volume.

The ingestion of sugar before exposure to an altitude of 27,000 feet, increases the tolerance of rats to anoxia by 40 per cent (34). This result, though not unexpected, clearly demonstrates that the sensitivity to anoxia is determined by other variables than that of partial pressure of oxygen alone. Sugar fed to rats, which have been severely anoxic for some time, produces a response that may well be termed an "anoxic diabetic" response (35). The administered sugar causes a profound hyperglycemia and glycosuria. In riboflavin deficient rats, anoxia does not increase the carbohydrate levels (36) but an injection of riboflavin into animals at reduced pressure restores the responses nearly to normal, indicating that riboflavin is important to carbohydrate metabolism during anoxia. In experiments on cats at 43,000 feet, it was found that the animals survive longer in mixtures of 75 per cent oxygen and 25 per cent carbon dioxide than they do in pure oxygen. Their resuscitation after exposure to 33,000 feet for five to fifteen minutes is accomplished with less difficulty by oxygen-carbon dioxide mixtures than with pure oxygen (37). Further experiments such as those quoted above are needed before all of the interrelations between oxygen, carbohydrate levels, and acid-base balance can be understood. It is sufficient to note now that the effect of lack

of oxygen is not simply related to the oxygen content of the blood.

Sickle cell anemia has been found to be without effect on the anoxic tolerance of negro flying cadets (38). "Sickling" therefore appears to be a defect in the red cell which does not interfere with the respiratory functions of the blood.

Pressure breathing.—The interest in pressure breathing continues, not only because of its applicability to flight at 35,000 to 50,000 feet, but also because of the applicability of pressure breathing apparatus to the maintenance of adequate gas exchange in many types of respiratory disease. A review has appeared which summarizes the results of the war studies and which gives detailed methods of appraising the effectiveness of a given pressure breathing system (39). Using a balistocardiograph to test the effect of pressure breathing devices on cardiac output, no reduction in cardiac output was seen at 46,000 to 50,000 feet, although a decrease was observed at sea level (40). This result is somewhat surprising as it indicates that pressure breathing at low densities of air is quite a different process than at normal densities. Subjectively, it has been noted often that pressure breathing is easier at altitude. Many of the adverse effects of continuous positive pressure, i.e., a decrease in cardiac output and a rise of venous pressure (41, 42), disappear if the proper cycle of pressures is applied (43). The gain in altitude with positive pressure is equal to what might be expected from the rise in partial pressure of the alveolar oxygen both theoretically and when subjected to experimental test (44). Visual function has been used to measure the gain in altitude (45). When a subject first goes on pressure breathing, there is a slight drop in finger temperature, probably the result of stimulation of receptors in the thoracic region by the altered pulmonary pressure relationships. However, this drop in temperature does not persist, indicating that pressure breathing would not be expected to interfere with temperature regulation per se (46).

Alveolar air.—Equations have been developed for calculating the alveolar air compositions in terms of the altitude, the composition of the inspired air, the alveolar ventilation volume, the rate of oxygen consumption and the respiratory quotient (47). These equations can be illustrated graphically on charts in which the partial pressure of alveolar carbon dioxide is plotted as an ordinate and the partial pressure of the alveolar oxygen as an abscissa. The quantitative relations thus developed aid greatly in understanding

many of the facts of high altitude physiology. For example, an increase in the ventilation at reduced oxygen pressures raises the alveolar oxygen pressure faster than the carbon dioxide partial pressure falls. This is equivalent to a temporary elevation of the respiratory quotient, as has already been demonstrated (48).

Determination of the effective alveolar oxygen and carbon dioxide pressures and the apparent gradient of the gas pressures through the lung can be made indirectly by a determination of the pressure of the carbon dioxide in arterial blood and the partial pressures of oxygen and carbon dioxide in the inspired and expired air (49). At sea level while at rest, the gradient for oxygen, calculated in the manner outlined above, averages 9 mm. Hg. During exercise, it increases to 16.5 mm. Hg. and there is no significant change in the apparent gradient under conditions of anoxia (50). At partial pressures of oxygen encountered at high altitude, however, the apparent gradient is largely the result of venous admixture. In anoxia, the gradient appears to be largely due to a true membrane resistance. A gradient of 36 mm. Hg. has been found in eight subjects when pure oxygen was inhaled (51), and from this data, it was calculated that the venous admixture could not be larger than 2 per cent.

Acclimatization.—It is claimed that young children and young animals do not adapt themselves as well to high altitudes as adults. It is believed that the adaptive mechanisms, which insure the resistance of the adult to mild anoxia, have not fully developed in young adolescent animals (52). Data continues to accumulate indicating that the adrenal gland of cats plays a large part in adapting animals to the stress of intermittent anoxia (53). The effectiveness of these adaptive mechanisms has been tested in man. Subjects taken to 12,000 feet daily for three hours for two to four weeks, showed an improvement of up to 7,000 feet in altitude tolerance as tested by the Schneider rebreathing test (54). This gain in altitude tolerance was not accompanied by any significant or demonstrable metabolic changes.

Careful research on the acclimatization process has been carried on at the Naval Air Station, Pensacola, Florida. Four men, housed in a small decompression chamber, were subjected to increasing degrees of anoxia over a five-week period (55). Extensive studies were undertaken of the effects of anoxia on respiration, acid-base balance of the blood, heart and circulatory system, exercise toler-

ance and other variables. It was found that the arterial carbon dioxide partial pressure dropped as low as 17 mm. Hg., while the arterial oxygen partial pressure after acclimatization to 20,000 feet was in the neighborhood of 30 mm. Hg. Another notable finding was the big decrease in exercise tolerance, much greater than would be expected from previous experience with mountaineers. This may be the result of the limited facilities for physical activity in the chamber situation. The respiratory and circulatory changes during the experiment seemed to be in the direction of preserving the cellular oxygen partial pressure, since there was a significant decline in the gradients of oxygen pressure existing between the external air and the tissues (56, 57). There was no evidence of a decline in oxgygen consumption. The various people who took part in the experiment deserve the greatest of credit, since "Operation Everest" is certain to become one of the classics of high altitude physiology.

One of the results of residence at high altitudes is an increase in the red cell count. If artificial polycythemia is produced by transfusion of red cells, an increase in the altitude tolerance by 5,000 feet, from estimates of pulse rate during exercise, is accomplished (58). The increase in tolerance was associated with the rise in the hematocrit from 46 per cent to 58 per cent. This demonstrates, for the first time by direct experiment, the fact that an increased red cell concentration helps combat anoxic-anoxia and that this is one of the important factors in acclimatization.

Exposure to altitudes as low as 8,000 to 10,000 feet for ten hours brings about changes in body economy, as indicated by the alkalinity of the urine, elevation of the respiratory quotient, and other factors more directly indicative of physiological deterioration. In these experiments, it was found that those subjects who had a high respiration quotient withstood the stress of anoxia in a better fashion (59).

A new concept in the process of adaptation has been brought forward. This presupposes that a partial change to anerobic sources of energy takes place during acclimatization and that the efficiency of these changes determines the degree of adaptation to anoxia (60). Only further experiments can throw light upon the fruitfulness of this suggestion.

Equipment.—The physiological oxygen requirements for flight to 40,000 feet can be said to be firmly established. However, more

ventilation data is sorely required before the best design of oxygen equipment can be determined. The magnitude of the minute volume of respiration and the pressure cycles during inspiration and expiration are important factors in such design (61). A practical comparison of the **BLB** and **RCAF** systems of oxygen supply show that there is little difference in the two systems, despite theoretical advantages of each (62).

The development of liquid oxygen systems for large aircraft continues. One system has functioned at 20,000 feet for fifteen hours completely automatically (63). An oxygen warning device which is well beyond the laboratory stage has also been described (64). Such a device has much in the way of safety precautions to recommend it. This system gives warning on a central panel of the conditions at all the oxygen outlets in an airplane, and information as to the welfare of individuals at these stations during their stay at "oxygen altitudes." Examination of the oxygen systems used by the Japanese in their airplanes demonstrates them to be much inferior to various American devices (65). One oxygen candle, used extensively by the Japanese, gave off appreciable amounts of carbon monoxide, a hazard not to be tolerated in any oxygen system.

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REGULATION OF ENERGY EXCHANGE[1]

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In order to summarize the field of energy metabolism as it appears today, a quite informal balance sheet has been drawn up, and upon it subjects have been entered under two headings, viz., (*a*) knowledge established by experiment or predictable from known data, and (*b*) concepts and hypotheses which require further study. Under the first heading appear the outstanding contributions of the past sixty years or more—development of methods and apparatus for the direct and indirect measurement of energy exchange and heat production; applicability of the laws of thermodynamics to biological systems; determination of the energy value of foodstuffs, and their efficiency of utilization in a thermodynamic sense (the specific dynamic action or S.D.A.); discovery of mechanisms of temperature regulation; variability of heat production, especially of the "basal metabolism," in response to almost every known type of environmental and physiological change; physiology of muscular exercise, including measurement of its efficiency; foundations of the physiological chemistry of energy metabolism; and finally, beginning knowledge of the physiology of energy storage as it occurs in young, growing animals, or in the adult during the accumulation of protein, carbohydrate and fat. With these discoveries are associated the names of Lavoisier, Voit, Rubner, Lusk, Atwater & Rosa, Benedict, DuBois, and scores of others privileged to share in establishing as a science the study of energy metabolism (1, 2, 3). That their investigations are of more than historical interest is clearly shown by the fact that the majority of the papers published in this field within the past two years represent almost direct continuation of research so profitably carried on in the late nineteenth and early twentieth centuries.

Under the second heading of the balance sheet are found at least two subjects which, in spite of the attention they have received, must be classified as either largely unknown, speculative, or controversial. One of them, the chemistry of energy exchange, will not be further considered in this review because it properly belongs in the *Annual Review of Biochemistry*. Nevertheless, it is a subject of great interest to physiologists, since it deals with the

[1] This review covers the period from July 1, 1945 to June 30, 1947.

chemical reactions through which occur the energy exchanges associated with irritability, conduction, contraction, secretion or concentration, and the synthesis of organic compounds. Ultimately it may be possible to give detailed accounts of the liberation of free energy and heat in the various cells, and thus to describe their ability to live and act (4 to 22).

More properly within the scope of this review, however, is the other subject, which may be identified as the regulation of biological energy exchange. Current interest in this subject was stimulated by the recent war, yet certain investigators, for example, Adolph (23), Brody (3), and their collaborators, had been for some years engaged in this type of study. While normal animals achieve from day to day a fairly constant energy balance, measurement of the four important variables concerned in this balance, viz., food, stored energy, work, and heat production, reveals that none of them is constant, but that each may perhaps increase at one time and decrease at another. Moreover, mammals appear to be able to make qualitative choices among these four, for example to increase or decrease their food intake and to dispose of more or less food energy as heat, as work, or as stored carbohydrate, protein and fat (24 to 27). Since little is known of the mechanisms responsible for this selectivity, further study seems to be in order, in the expectation that whatever may be learned will have an importance both academic and utilitarian (28 to 34).

Two general types of reactions appear to participate in the regulation of energy exchange. One, physical regulation, was mentioned by Brody [(3), p. 246], who noted that upon a given food intake, body weight is self-limited by physical laws, in that with every increase in body size, basal heat production rises until the animal reaches a size where its total heat loss equals its energy intake, and no surplus remains for growth or storage. When an animal is fed ad libitum, however, physiological mechanisms become equally important. As the animal grows, it does not maintain a constant intake, but rather increases its intake throughout the growth period. That the intake increases as the animal becomes larger could not be predicted from known physical laws, nor could one foretell on this basis the relative proportions of carbohydrate, fat and protein to be stored during growth. As Kleiber (35) pointed out, a living organism is capable of selections among variables in a fashion not dealt with by the so-called laws of thermodynamics.

Energy Storage

To review adequately the regulation of body size, one must refer to other articles in this volume and in previous volumes of the series, particularly, to chapters on growth and development. Experimental embryologists and endocrinologists have gained valuable insight into at least some of the mechanisms regulating growth (36), as well as factors determining what class of compound will be stored at different stages. Moreover, since growth of bacteria, protozoa, and all other animals is subject to certain regulations, it is to be expected that through study of simple forms the reactions of more complex species will be made more comprehensible (37, 38). Mammals seem to differ from lower forms mainly in the relatively greater importance assumed by specialized cells of the nervous and endocrine systems through whose activity patterns of growth or integrated growth is made possible (39, 40).

Related in many ways to growth are the processes through which an adult accumulates stores of carbohydrate, protein and fat; for discussion of the regulation of each of these, the reader is referred to Brody's monograph (3), and to appropriate reviews elsewhere. Protein storage or nitrogen retention has been intensively studied recently, and the ability of hormones of the anterior lobe of the hypophysis and the adrenal cortex to influence nitrogen retention is thoroughly established (41 to 44). No less interesting is the nitrogen retention which follows injection of androgens (45, 46), and the observation that the effect is not mediated entirely through the pituitary gland (47, 48). Many laboratories are studying nitrogen balance as it is affected by composition of the diet, the ability of different proteins and protein derivatives to produce nitrogen retention (49 to 62), and the influence of the nonprotein portion of the diet upon protein storage (63 to 65).

Regulation of fat storage now appears to be a passive process, subject only indirectly to control. Presumably the fatty depots increase in size whenever energy intake exceeds total output, and decrease when the situation is reversed (66, 67). If this is true, the quantity of fat in the body is determined by mechanisms which regulate food intake, work (or activity) and body temperature, and inquiry into the pathogenesis of human obesity must seek to discover abnormalities in the regulation of one or more of these factors. Excessive food intake seems to be the most common abnormality (68, 69), and although there is no general agreement as to the nature of the regulatory deficit (70, 71, 72), the impor-

tance of psychic and emotional factors is often stressed (73, 74). (Food intake is more fully considered below.)

Data upon the opposite state, i.e., emaciation due to starvation, continue to be reported (75 to 78), revealing to those of us who were more fortunate something of the misery and suffering undergone by prisoners of war (79 to 82).

Body Temperature

Regulation of body heat exchange has been studied more successfully, perhaps, than any other regulation except that of water exchange. In accordance with the outline of Rubner, reactions are usually classified as physical or chemical, the former of which includes those of heat loss, and the latter, those of heat production which may be further subdivided into basal heat production, and heat liberated in the course of food utilization, exercise, and resistance to thermal stress. Recent experiments supplement what is already known regarding basal heat production and its variations (83 to 94), as well as the role of the thyroid gland in the control of metabolic function (95 to 105). Of unusual interest is the collection of papers published together in 1945 upon the subject, "Preparation and biological effects of iodinated proteins" (106 to 112). Of equal interest are data upon the heat production during food assimilation (113, 114), and therapeutic use of the S.D.A. as a means of provoking peripheral vasodilatation (115, 116). This heat of metabolism appears to be a mild heat stress, which is dissipated through an increased cutaneous circulation. In a thermodynamic sense, the S.D.A. is the important determinant of efficiency of food utilization (in spite of the fact that other definitions of efficiency have been introduced into nutrition). Forbes and his collaborators (117 to 121) have shown that both growing and mature rats have more energy available for storage and waste less as heat upon diets high in fat (30 per cent by weight) than upon diets lower in fat content (2 per cent by weight). This difference between the diets appeared during isocaloric feeding, and was accounted for by the greater S.D.A. of the low-fat diets. Their results have been confirmed in a general way by Deuel *et al.* (122 to 124), who found that upon ad libitum feeding, rats ate more food when fed mixtures high in fat content (up to 50 per cent by weight, 70 per cent by calories). Relatively large amounts of fat in the diet, therefore, alter the efficiency of food utilization as well as the regulation of food intake in a direction which leads to the

storage of extra energy as fat. This extra gain appears to be advantageous to the animal, and it is not difficult to visualize situations (e.g., starvation) where the fat-fed individual would have an advantage over his less well provisioned control. This would be equally true in recovery from undernutrition (123 to 125). Furthermore, rats on the diets higher in fat content appeared to possess somewhat greater physical capacity, measured in this instance by a swimming test (122).

Investigation of the efficiency of muscular exercise is another important phase of energy metabolism (126 to 130), but further data on this subject must be sought elsewhere.

One of the ways in which study of body temperature has advanced further than study of other regulations may be illustrated by noting that one can now localize fairly well the specialized cells responsible for controlling rates of heat exchange. Following Barbour's (131) pioneer experiments, Magoun *et al.* (132) and Beaton and his collaborators (133) localized within the anterior hypothalamus and preoptic region of cats and monkeys a heat-sensitive mechanism, capable of initiating polypnea, panting and sweating. In their opinion this mechanism responded to slight changes in the heat content of blood prefusing the base of the brain. On the other hand, Bazett (134, 135) directed attention also to the possibility that temperature-sensitive nerve endings in the skin participate in the regulation. It now seems likely that each of these mechanisms has its place (137), since Adolph (136) has observed conditions under which the central mechanism appeared to become active without change in skin temperature. Role of the central mechanism as a thermostat is further emphasized by data which indicate that the level at which body temperature is maintained is influenced by a variety of substances, including sodium, potassium and magnesium ions, toxins and progesterone (138 to 142).

Spontaneous Activity

Activity or work output is another of the broad categories of energy exchange subject to physiological regulation, but this has been little studied in human subjects, since most of the research upon exercise has concerned either physiological reactions to given work loads, or maximal ability to work (126 to 130, 143 to 146). Regulation, on the other hand, implies "willingness" to work or voluntary work output, which is well typified by an experiment performed upon German working men during the war (147). When

only limited quantities of food were available, work output was found to be proportional to the level of energy intake, although strongly influenced also by a psychological factor in the nature of "incentive pay." Cigarettes promised to the men in return for extra work evoked a sharp rise in their output, accompanied by a loss of body weight as they drew upon their stored energy reserves. From earlier experiments performed upon laboratory animals by Slonaker (148), Richter (149, 150), Browman (151) and others, one may conclude that environmental temperature, lighting, composition of the diet, and function of various endocrine glands all influence the level of spontaneous locomotor activity. Moreover, there are many observations pointing to the existence of controlling mechanisms within the central nervous system (152 to 155). Sleep, the lowest activity level of a normal animal, depends in some way upon the hypothalamus (156, 157), while hypoactivity regularly follows production of posterior hypothalamic lesions (158). By contrast, hyperactivity can be produced by ablation of the frontal lobes (159, 160), or specifically by removal of area 13 of the orbital surfaces (161). It has been suggested, therefore, that the base of the brain regulates locomotor activity and possibly even willingness to work; the concept, however, is a hypothetical one, valuable only as it may assist further research.

Food Intake

Regulation of food intake is not peculiar to mammals (162, 163) although their reactions are the more complex because they involve interactions among highly specialized cells. The studies of Cannon & Washburn (164) and Carlson (165), widely accepted, have led to a tendency to assume that the stomach [and possibly the duodenum (166)] is the organ where hunger and satiety originate, responsible for maintaining the balance between energy intake and output. Since Carlson found that gastric denervation did not prevent the appearance of hunger contractions, a virtual autonomy in this function has been ascribed to the stomach. This concept, however, was criticized by Hoelzel (167), and more recently by Grossman *et al.*(168), and Harris and his colleagues (169), who found that vagotomy and abdominal sympathectomy did not disturb the regulation of food intake, nor did it prevent the development of insulin-induced hyperphagia or of amphetamine induced anorexia. They suggested, as Hoelzel had done in 1927, that hunger is a central phenomenon. Historically a very old

concept (165), this suggestion gains support from a number of related experiments, even from Carlson's observation that he occasionally experienced a desire for food when no gastric contraction was in progress [(165) p. 212], and that gastric contractions sometimes failed to evoke true hunger [(165) p. 94]. Now Adolph (170) and Ershoff & McWilliams (171) have clearly shown that animals adjust their food intake to the nutritive density of the diet, while Strominger (172) has found regulation of food intake to be related to that of water intake, both in normal animals and rats with hypothalamic hyperphagia. All of these data imply that the animal does not eat simply to fill its gastrointestinal tract, since variable quantities of water or of indigestible bulk are properly compensated for. One is impressed by the precision with which the mammalian organism adapts its food intake, whether to a change of environmental temperature (173, 174, 175), or to other types of change (176). From experiments in which rats were allowed to choose the various components of their diet, Scott & Quint (177 to 180) have concluded that this adaptation involves learning processes in which certain animals appear to be deficient.

In spite of the present tendency to minimize the significance of gastric hunger, the observations of Cannon and Washburn, and of Carlson, as well as of many others who have repeated their work, cannot easily be disregarded. Perhaps the two views can be reconciled, and what appear to be conflicting data can be used to give a reasonable explanation of over-all regulation of food intake. If one were to grant the possibility that both sets of observations are correct and that both central and peripheral reactions are associated with taking of food, one might infer that the interpretation placed by the central nervous system upon sensations arriving from the gut, or even the central threshold for these sensations, is determined by the central state. Thus, if the central state is one of "hunger" or "appetite," any sensation produced by hunger contractions only serves to intensify the animal's awareness of need for food, while if sensations coming from the gut are evoked by distention (e.g., with a balloon), the nervous system separates the two experiences and interprets them as desire for food in spite of gastrointestinal fulness. On the other hand, if the central state is one of "satiety," fulness of the stomach will reinforce the satiation, while gastric contractions may be interpreted as painful cramps, or even as provocative of nausea and vomiting.

Harris, Ivy & Searle's data (169) upon the central action of

amphetamine are supplemented by those of other workers, which seem to point to the existence of a central mechanism whose function may be altered by administration of various substances (181, 182, 183). That this mechanism includes at least a part of the hypothalamus is indicated again by the well conceived experiments of Brooks and his collaborators (184, 185, 186), and possibly also by Ronald's report (187) of two cases in which hypersomnia was associated with abnormal hunger.

In conclusion, a word may be added regarding the significance of these mechanisms of regulation. Claude Bernard and Walter Cannon were responsible for turning the attention of physiologists to the relative constancy of composition of the internal environment and the efficiency of mechanisms which kept it so. A few years ago interest in the whole subject of exchanges was reawakened by the work of Schoenheimer and his co-workers, while study of regulations quite naturally gained impetus also from the publication of Adolph's monograph upon that subject. The organism maintains continuous thermodynamic exchanges just as it carries on exchanges of water, oxygen, carbon, nitrogen and other elements and compounds. Consequently, it might be in order to suggest that what has been learned about certain other regulations may be applied by inference to energy metabolism. For carbon dioxide, water and heat, regulation of the rates of exchange in mammals is known to be accomplished by the complementary action of two types of mechanisms, namely, effector systems capable of carrying out the exchange, and sensitive cells capable of reacting to concentration gradients of the individual substances. Thus, the lungs and respiratory muscles are effector organs for carbon dioxide exchange, while the sensitive cells include part of the respiratory center and the other chemoreceptors which govern rate and depth of respiration. The kidney is an important organ of water excretion, which is regulated by sensitive cells (possibly neurons of the supraoptic nucleus) which control the rate of output of the antidiuretic hormone (188, 189, 190). If this analogy be extended to energy metabolism, the effector organs become the skeletal muscles, the abdominal viscera including the gastrointestinal tract, the skin, and the body's depots for protein, fat and carbohydrate; this much is known and generally agreed upon. What is not known is the location and identity of cells capable of regulating the various exchanges carried out by these organs, and the nature of the changes in body fluids or the concentration gradients

to which the sensitive cells respond. For example, if there is indeed a central regulation of food intake, it must depend upon some reversible change which occurs during assimilation of food, a change able to activate or to inhibit the sensitive cells. At the one extreme this change presumably evokes a feeling of desire for food, at the other, a feeling of satiety. The nature of this change, where it occurs, how it is perceived and its significance made apparent to the organism remain to be discovered.

Much of this material on the possible nature of the regulations obviously must be entered on the balance sheet under the heading, speculative or unknown. Although the significance seems clear enough, most of the concepts presented here remain to be either established or disproved in the laboratory.[2]

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METABOLIC FUNCTIONS OF THE ENDOCRINE GLANDS*[1]

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In his inaugural address as the first president of the new Society for Endocrinology in Great Britain, Harington (107) has selected as his subject *The Scientific Foundations of Endocrinology.* He relates how much of our present knowledge of the thyroid has been dependent on the contributions of natural historians, geographers and geologists, physicians and surgeons, biologists and pathologists, chemists, biochemists and physicists. The history of research on the thyroid, as he has presented it, is an admirable example of the multiple scientific foundations of the entire endocrine system. Houssay (116), in a chapter entitled "Hormones," in *Currents in Biochemical Research,* has given the outline of the superstructure of this new science, Endocrinology. Dodds (73) has added the personal history of some of its builders in an address entitled *Stories in Endocrinology.* Dodds closes his address as follows:

> My object in this lecture has been to show that research is never done as it is written, and that the cold orderly paper is produced practically always by a series of blundering steps in which the research-worker is rather like someone in a dark room scrambling for the switch and tripping over the furniture. When he has once found the switch and turned on the light, he can arrange the furniture in orderly fashion.

Thyrotropic[4] Hormone and Thyroid

Several excellent reviews have appeared on various aspects of thyroid physiology: Rawson & McArthur (195) and Keating (135)

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[4] The Editors of the Annual Reviews prefer the suffix "tropic" and they are endeavoring to observe this convention uniformly throughout the Annual Reviews. The author of the present article prefers "trophic" and has requested the insertion of a footnote to this effect.

on radio iodine in the study of the thyroid, Roth (202) on the action of thyroid hormone and of substances antagonistic to it, Fleischman (85) on comparative physiology of the thyroid, Reineke (197) on thyro-active iodinated proteins, Salter (207) on circulating thyroid hormone, and Mahaux (163), a monograph entitled *Essai de Physiopathologie Thyro-Hypophysaire.*

Thyroid hormone.—A variety of studies have been carried out on problems related to thyroxine formation in the body. Dvoskin (79) has shown that the subcutaneous injection of elemental iodine (I_2) into the rat and chick has a thyroxine-like action: e. g., in young thyroidectomized female rats it reinitiates bone growth and causes increase in body length, while in the intact rat it causes a marked decrease in cell height of the thyroid epithelium and a decrease in the weight of the thyroid gland; in thiouracil-fed chicks it causes complete inhibition of the goitrogen. Chaikoff, Taurog & Reinhardt (53) have shown in rats that a fall in the level of protein-bound iodine in the plasma is apparent within four hours after thyroidectomy and that the minimum level is reached by the third day; on the other hand, thyrotropic hormone raises the level of protein-bound iodine in plasma. The rate of incorporation of radio inorganic iodine into the protein-bound fraction of iodine in plasma is decreased or increased as the levels of protein-bound iodine change with thyroidectomy or thyrotropic stimulation. Taurog, Chaikoff & Entenman (225) have estimated the rate of turnover of protein-bound iodine in the plasma of the dog to be from four to seven and one-half hours.

Wooley (251) has reviewed the recent advances in the study of compounds which are structurally similar to but biologically antagonistic to metabolically important substances. These compounds, which act in competition with vitamins, hormones or other metabolites, act by producing signs of deficiency of the metabolite to which they bear structural resemblance. Wooley (250) has prepared several ethers of N-acetyldiiodotyrosine which counteract the pharmacological effect of thyroxine in tadpoles. In a study of the antigenic properties of iodinated proteins, Parkes (180) found that precipitates resulting from reactions between iodinated proteins and antisera thereto, showed thyroidal activity in the test on Xenopus tadpoles, but only a small amount of the total original activity of the antigen was detected in the precipitates.

Thyroid and vitamins.—Sadhu & Brody (203) have reported their findings on the action of vitamin A and the thyroid. The feeding of an excess of vitamin A depressed the basal metabolism and reduced the weight of the thyroid in rats; it tended to neutralize the metabolic effects of injected thyroxine and decreased the size of the thyroid in thiouracil-treated rats. They have suggested, as an explanation of these effects, that the thyroxine iodine is taken up by the double bond of the vitamin A which removes the metabolism-stimulating effects of thyroxine, and that the iodinated vitamin A depresses the thyrotropic hormone secretion of the pituitary. Drill & Truant (77) have shown that thyroidectomized rats have an impairment in their ability to convert carotene to vitamin A. Ershoff (84) has reported on the benefit of liver feeding in counteracting the retardation of growth and the inhibition of ovarian development which occur in immature rats fed toxic amounts of desiccated thyroid.

Histophysiology of the thyroid.—Bélanger & Leblond (27) have described an autographic method for histological localization of radio elements in tissues, which consists of covering the sections containing radio-active material with a photographic gelatin emulsion, and after a sufficient exposure to the rays of the radio element, developing the "autograph." The section can then be stained through the gelatin coating by the usual techniques. This method has been used successfully with thyroid tissue containing radio iodine. Dempsey & Singer (69) have studied various chemical cytological reactions in the thyroid under different functional states; Wahlberg (239) has described the histophysiology of the thyroid in cases of thyrotoxicosis; Junqueira (133) has made a cytological study of fragments of thyroid gland after incubation for periods up to ninety-six hours with thyrotropic hormone and iodides. An interesting study on the functional behavior of thyroid nodules has been made by Puppel, Leblond & Curtis (189). They found that all nodules which they studied had a decreased function when compared to the function of the corresponding paranodular thyroid tissue, there being less avidity for administered radio iodine and a lowered production of thyroxine and diiodotyrosine. Diffuse goitrous tissue of patients with nontoxic diffuse colloid goiter showed great avidity for iodine, but its ability to produce thyroxine and diiodotryrosine did not appear greatly increased. The diffuse hyperplastic tissue in exophthalmic goiter displayed

the greatest avidity for iodine and the greatest ability to produce thyroxine and diiodotyrosine. In contrast to the findings of Puppel *et al.*, Cope, Rawson & McArthur (56) observed thyrotoxicosis due to a hyperfunctioning single adenoma in twelve patients.

Thyrotropic hormone.—Two excellent reviews on the thyrotropic hormone have appeared, by Adams (1) and Borell (31). Adams has summarized the data on the variations in potency of the thyrotropic hormone of the pituitary and of the body fluids. A change in potency follows a variety of experimental conditions: (*a*) removal of certain endocrine glands, especially thyroid, gonads and adrenals, or administration of their hormones; (*b*) modifications in diet, especially the administration of goitrogenic foods or drugs; and (*c*) subjection of animals to changes in external environment, such as pressure and temperature. A balanced relationship between the production of thyrotropic hormone and of thyroid hormone appears to be a fundamental mechanism. It seems likely that the nervous system may be involved in the changes induced by external environment. The concept of a thyroid-inhibiting action of the pituitaries of rats treated with desiccated thyroid, which was proposed by Reforzo-Membrives (196), has not been confirmed by Purves & Griesbach (192). Borell's (31) review entitled, *On the Transport Route of the Thyrotrophic Hormone, the Occurrence of the Latter in Different Parts of the Brain and its Effect on the Thyroidea*, describes the methods of detecting small quantities of thyrotropic hormone. Of particular interest is the finding of a thyroid-stimulating substance in the tuber cinereum and choroid plexus. This substance is increased in amount when the animals are exposed to cold and disappears entirely after hypophysectomy. The author concludes that the thyroid-stimulating substance in the tuber cinereum and choroid plexus is the thyrotropic hormone of the anterior pituitary which has been transported via the stalk of the hypophysis to the tuber cinereum and from there into the choroid plexus by way of the III ventricle.

Inactivation of thyrotropic hormone by iodine has been reported by two independent groups of workers, Wright & Trikojus (254) and Albert and co-workers (6). Both demonstrated that the addition of free iodine (I_2) to preparations of thyrotropic hormone resulted in complete disappearance of the thyrotropic activity. The latter group showed also that the inactivated preparation could be restored to its original thyrotropic potency by trituration in an

excess of acetone. Wright & Trikojus were unable to restore thyrotropic activity by the method which they used. Albert *et al.* (7) reported also that the inactivated hormonal material could be restored to activity by treatment with various goitrogenic and non-goitrogenic reducing compounds, such as thiouracil, ascorbic acid, potassium cyanide, sodium thiosulfate, and aminothiazole. They showed further (8) that augmentation of thyrotropic potency was brought about by mixing pituitary extract with these goitrogenic compounds. The augmenting effect was not abolished when the goitrogenic substances were presumably removed from the hormone prior to bioassay. Borell & Holmgren (32) and Crabtree & Trikojus (59) have found that ascorbic acid does not influence the effect of thyrotropic hormone on the thyroid nor on the level of liver glycogen.

Action of antithyroid drugs.—One of the important contributions on the action of antithyroid drugs is by MacKenzie (156), who with McCollum and MacKenzie was responsible for initiating the problem of antithyroid drugs in 1941. In this latest report he has reviewed the subject since 1941. The facts which seem to be generally accepted at present are: (*a*) that thiourea and the sulfonamides depress thyroxine formation; (*b*) that the thyroid hyperplasia (the goitrogenic effect) is due to an increased secretion of thyrotropic hormone secondary to the inhibition of thyroid hormone production; (*c*) that the oxidation of iodide to iodine is the essential biochemical step in the natural formation of thyroxine (107, 108); and (*d*) that sulfhydryl compounds such as thiourea and thiouracil readily reduce iodine to iodide (47, 171, 243). By studying the difference in response to iodide of the sulfa-guanidine-treated and the thiouracil-treated rat MacKenzie has postulated different biochemical reactions for the two drugs. If the antithyroid action of thiouracil is due to the prevention of the formation of appreciable amounts of iodine in the thyroid, the addition of small amounts of iodide should decrease the goitrogenic effect of thiouracil by increasing the formation of iodine by a mass action. By the use of critical conditions for revealing an effect of iodide, MacKenzie found that small amounts of iodide inhibited the goitrogenic action of thiouracil by 50 to 100 per cent, depending upon the level of thiouracil used. The level of iodide is exceedingly important in this connection, Purves & Griesbach (190), for instance, having found that a high iodide concentration acts synergistically

with thiourea in depressing thyroxine synthesis in the rat. According to MacKenzie, the goitrogenic action of sulfaguanidine, on the other hand, would seem to be dependent upon a different mechanism. Addition of iodide augments the goitrogenic effect of low levels of sulfaguanidine. Since the addition of iodide to sulfaguanidine appears to exert no mass action effect on the chain of reactions leading to thyroxin synthesis, it would seem that the sulfonamides inhibited an essential enzyme in the chain of reactions. Small amounts of iodide also inhibit the goitrogenic effect of *p*-aminobenzoic acid.

Randall (193) has shown that the antithyroid activity of some thiol compounds cannot be explained by their antiperoxidase activity. Thiol compounds do not inhibit peroxidase, but, on the contrary, are substrate for the peroxidase-hydrogen peroxide. Thiol compounds are oxidized by hydrogen peroxide and the rate is accelerated by peroxidase. McShan, Meyer & Johansson (161) and Glock (100) have shown that the prevention of thyroxine synthesis within the thyroid by thiourea and thiouracil is not due to the inhibition of cytochrome oxidase activity. Tipton & Nixon (230) found that thiouracil does not depress the activity of succinoxidase or cytochrome oxidase in the liver directly, but rather, indirectly, by depressing thyroid hormone production. Thiocyanate, another goitrogenic drug, inhibits the iodine concentrating capacity of the thyroid [Wolff *et al.*, (249), Vanderlaan & Bissell (234), Vanderlaan & Vanderlaan (235)]. The goitrogenic effect of this drug is abolished by the administration of sufficient iodide.

In a recent letter to *Lancet*, Biancalana (29) has called attention to the use of sodium thiosulfate as an antithyroid drug. Since 1943 he has successfully treated patients suffering from thyrotoxicosis with intravenous injections of sodium thiosulfate. Another interesting observation is that of Lawson & Remington (141) that ergothioneine, a normal constituent of red blood cells, is of the same chemical type as thiouracil and is comparable with it in antithyroid activity.

Effects of antithyroid drugs.—McQuillan & Trikojus (160) have studied the effect of thiourea on the guinea pig thyroid when given concurrent with and subsequent to the prolonged administration of thyrotropic hormone. It was found that the development of a refractory state to thyrotropic hormone prepared from ox pituitary prevented, or at least significantly reduced, the response of the

guinea pig's thyroid to thiourea. The authors suggest that the development of immune bodies (thyrotropic antihormone) in response to a heterologous thyrotropic hormone inhibited the animal's own thyrotropic hormone sufficiently to prevent the hyperplasia normally found with thiourea administration. Another observation in this series of experiments was the reduction in the relative size of the adrenal glands as treatment with thiourea was prolonged. This is in agreement with the findings of certain workers (22, 99, 145); however, Richter & Clisby (198) and more recently, Leathem (144), observed no changes in the adrenal gland of rats treated with thiourylene drugs. The difference in findings may well be due to the differences in the amount of drug administered and the duration of the treatment.

Purves & Griesbach (190) have adduced evidence to show that thiourea inhibits extrathyroidal thyroxine synthesis. They have shown that total thyroidectomy in rats induces changes in both the basophils and acidophils: there is a marked increase in the numbers and size of the basophil cells; the acidophils, on the other hand, lose their acidophil granules and become almost indistinguishable from chromophobe cells. The basophils, according to these workers (103), are the producers of thyrotropic hormone and their prompt increase in numbers under conditions of the slightest thyroxin deficiency is due to a highly sensitive homeostatic mechanism affecting the pituitary-thyroid relations. These authors have shown also that large amounts of iodide in completely thyroidectomized rats have a protective action on the acidophil granules similar to that of small amounts of thyroxine. This suggests extrathyroidal synthesis of thyroxin from the injected iodide, and would support the earlier findings of Morton *et al.* (173) of the synthesis of minute amounts of thyroxine in completely thyroidectomized rats. When the thyroidectomized rats received iodide plus thiourea, there was complete degranulation of acidophil cells, suggesting that the thiourea had inhibited the extrathyroidal synthesis of thyroxine from iodide.

The surprising finding that beagle puppies do not need thyroid hormone under normal conditions has been reported by Mayer (167). Beagle puppies of two litters were fed propylthiouracil (30 mg. per kg. body weight) from the fifth or sixth week of age until sacrificed at six and one half to eight months. During this period no differences could be noted between the experimental puppies and

their litter mate controls of the same sex, with respect to rate of growth, ossification of tibial epiphysis and ribs, general health, appearance and behavior, amount of subcutaneous and intra-abdominal fat and relative weights of internal organs. The only effect of propylthiouracil observed was a retardation in the development of spermatogenesis, which was compensated after the seventh month. The thyroid glands at necropsy showed pronounced hyperplasia. Engle *et al.* (17, 83) have noted a similar response in monkeys. Thiouracil was administered to four adult female rhesus monkeys in increased doses up to 0.8 gm. each day for fourteen months. The clinical evidence of hypothyroidism was slight, although the thyroid glands showed severe hyperplasia. Danowski, Man & Winkler (64) found that the precipitable serum iodine in normal adult dogs ranged from zero to 2.4 gamma per cent. It is inconceivable that growing dogs or adult female monkeys need no thyroid hormone, but it would seem from these reports that the hormone requirement is exceedingly small.

Seegaţ Jones, Delfs & Foote (214) have shown that hypothyroidism induced by thiouracil has no effect upon the reproductive system of the adult male rat as judged by the ability to sire litters. However, Mayer (167) has found that propylthiouracil delayed the onset of spermatogenesis in young dogs. Prolonged thiouracil administration in the adult female rats did not cause sterility, according to Seegar Jones *et al.* (214), but it did have a marked effect upon the continuation of gestation, leading to resorption of fetuses in mid-pregnancy or late pregnancy. When the drug was given for less than 100 days some of the rats delivered litters which were normal in growth and development. Freiesleben & Kjerulf-Jensen (93) have demonstrated the placental transmission of thiouracil. Fetuses of pregnant rats which had been given thiouracil were fed to normal rats and hyperplasia of the thyroid demonstrated. These workers have also demonstrated cretinism in young rats and rabbits which had been suckled by mothers fed propylthiouracil.

Alpha-naphthylthiourea causes inhibition of hair growth and skin pigmentation in black rats. Phenylthiourea does not affect hair growth, but does inhibit skin pigmentation [Dieke (71)]. The mechanism by which these changes occur is not as yet understood. The changes in pigmentation induced in the plumage of fowls by thiouracil administration can be counteracted by simul-

taneous administration of thyroxine (132). Grossowicz (104) introduced thiourea into the yolk sac of Leghorn embryos of seven to seventeen days. This treatment retarded development and delayed hatching of the embryos up to ten days. Purves & Griesbach (191) have produced thyroid carcinomata in rats by treatment with thiourea.

Thiouracil as a therapeutic agent in the treatment of hyperthyroidism has been evaluated by numerous authors (24, 52, 114, 161, 162, 201, 247). Warnings in regard to the toxicity of thiouracil in patients have also been sounded (25, 90, 165, 172). Propylthiouracil is, at present, recommended as the safest and most effective antithyroid drug for clinical use (18, 26, 158). The pathologic changes occurring as a result of large doses of thiouracil have been described by McClosky, Lillie & Smith (157). Thiouracil fed to cats in doses as high as 300 mg. per kg. per day for a period of seven to eight months had no demonstrable toxic effects. Daily doses of 500 mg. per kg. in three cats proved fatal in thirty-eight to ninety days. The pathologic findings consisted of necrosis and scarring in the reticular zone of the adrenal cortex, moderate fatty degeneration in the liver with preservation of glycogen, atrophy of the thyroid and of the seminiferous tubules of the testis, hyperplasia of testicular interstitial cells, and moderate hepatic and splenic hemosiderosis.

Hypothyroidism and hyperthyroidism.—Hurxthal & Musulin (121) have reviewed the subject of cretinism, and Bastenie (21) has discussed the etiology of spontaneous myxedema in the adult. Foldes & Murphy (87) showed that plasma phospholipid phosphorus as well as cholesterol and cholesterol ester is significantly increased in hypothyroidism. Gordon *et al.* (102) found that the bone marrow of thyroidectomized rats showed a slightly greater state of hypoplasia and a lower erythroid-myeloid cell ratio than normal. Crafts (60) was able to prevent the microcytic hypochromic type of anemia which occurs after hypophysectomy in the rat by the administration of thyroxine, iron and copper. Mild hyperthyroidism in chickens induced by feeding thyroprotein increases egg production during spring and summer and also increases the yearly production during the third, fourth and fifth years [Turner & Kempster (233)]. Tissiéres (232) has shown a decrease in cytochrome-*c* in skeletal muscle in hypothyroid rats, and that it may be increased above normal with thyroxine. It is also lowered

after adrenalectomy. Lederer (146) has reported a case of hyperthyroidism in a girl six years old in which there was accelerated growth, advanced bone age and eruption of teeth and osteoporosis.

Adrenocorticotropic Hormone and Adrenal Cortex

Some of the important aspects of the chemistry and physiology of the adrenal hormones have been reviewed by Kendall (137), Gallagher (97), Long (150) and Pincus (186) in the *Proceedings of the Laurentian Hormone Conference.* Attention is also called to a monograph by Mellgren (168) on the *Anterior Pituitary in Hyperfunction of the Adrenal Cortex.*

Morphology of adrenal cortex and correlation with chemical changes.—Two papers (23, 68) on the histology of the adrenal cortex of the rat tend to disprove the theory of Salmon & Zwemer (204) that the glandular elements of the cortex originate in the capsule. By intravitam trypan blue, Baxter (23) observed that most of the cells of the peripheral part of the cortex (i. e., capsule, zona glomerulosa, and outer part of zona fasciculata) segregate trypan blue, commencing during the first twenty-four hours and reaching a maximum in forty-eight hours. Once established in the cell cytoplasm, the particles of trypan blue persist up to twenty one days. There was no evidence that any of the dye-containing cells migrated from the capsule. In colchicine-treated rats the number of mitotic figures per ten thousand cells was determined for each cortical zone. The highest mitotic rates were found in the zona fasciculata, then the zona glomerulosa; those in the zona reticularis and the capsule were considerably lower. Deane & Greep (68), in a morphological and histochemical study of the adrenal cortex after hypophysectomy, came to a similar conclusion regarding the independence of the two outer zones of the cortex. They showed that the "ketosteroids" gradually disappear from the zona fasciculata, but persist in the zona glomerulosa after hypophysectomy. The mitochondria also change in the fasciculata but not in the glomerulosa. Examination of the livers for lipids and glycogen revealed a reduction in liver glycogen, and by the fifty-sixth day post-hypophysectomy, complete disappearance. Individual cells were overfatty. It is unfortunate that this very fine work on the morphology of the adrenal cortex should be marred by the unwarranted conclusion of the authors:

These facts indicate that the carbohydrate-regulating principles of the adrenal

cortex which are under pituitary control are secreted by the fasciculata, while the salt-regulating fractions which are not entirely under pituitary control are probably formed in the glomerulosa.

Pathologic changes in the adrenal have been described by Cleghorn (54) in dogs which died as a result of muscle trauma. The adrenals of a dog dying one-half hour after trauma showed packing of red blood cells in the small vessels between the zona fasciculata and zona reticularis of the cortex. A more or less widespread invasion of the cortex by leucocytes was often seen in dogs dying a little later. Diffuse hemorrhages in the cortex were observed in the dogs dying three to five hours after trauma, reaching a maximum in dogs that died after ten hours. Swelling and degeneration of the cells of the inner two zones of the gland and a heavy distribution of leucocytes were constant features in such cases. These changes were not due to a lowered blood pressure, for they were seen also in dogs in which the blood pressure had been maintained at 110 mm. Hg. Cameron & Carmichael (48) believe that enlargement of the adrenals produced in the pre-mortem stage of acute starvation (withholding all food but not water for six days) is a pathologic process and not hypertrophy. The enlarged glands contained an increased amount of water, although their solid content remained practically unaltered, suggesting that the changes represented an increase in water content of the cells. This was shown by counting the nuclei of the cells in comparable areas and observing less nuclei per unit area in the adrenals of starved rats than in the controls. The glomerular zone was diminished in thickness and the reticular zone also showed abnormality.

Ludewig & Chanutin (151) have studied the chemical changes in rats' adrenals after injection of four types of beta-chloroethyl vesicants. The animals were sacrificed at daily intervals. Very few survived more than five days. During the five days the adrenal weight per 100 gm. body weight in the treated animals gradually increased. The adrenal enlargement was due chiefly to an increased water content and, to some extent, to protein and phospholipid increase. The total lipid concentration was decreased. A reduction of total cholesterol concentration was ascribed chiefly to the loss of ester cholesterol. If this lowering is due to the elaboration and release of adrenal cortical hormone, it is presumed that the esterified cholesterol is its precursor.

Effect of steroid hormones on adrenal cortex.—Cameron, Guthrie

& Carmichael (49) have called attention to the conflicting reports on the effect of estrogens on the adrenal cortex. In their own studies it was found that both estradiol and stilbestrol generally caused enlargement of the adrenals in male rats, and occasionally in female rats. In analyzing the nature of the enlargement they found an increase in water content and a decrease in the number of cells in the outer part of the cortex, as determined by actual counts in corresponding areas. These authors express the view that the estrogens produce no hypertrophy of the adrenals, but rather, in the dosage used (3 mg. estradiol or 3 to 6 mg. stilbestrol daily), something in the nature of a pathologic change. In mild chronic starvation the adrenals were never enlarged; from this it was deduced that the changes in the adrenal following treatment were due to the estrogens and not due to the decreased food intake which the estrogens caused. Negative findings on the effect of stilbestrol and testosterone on the adrenals of Brown Leghorn hens have been observed by Kar (134). Wooley & Little (252) have reported the effectiveness of stilbestrol in preventing adrenal cortical carcinoma which is normally expected to occur in both sexes of a special strain of mice if they have been gonadectomized soon after birth.

Pituitary-adrenal regulatory mechanism.—Sayers & Sayers (210, 211) have studied the regulatory mechanism of the pituitary-adrenal system which operates in the animal in response to stress. They have demonstrated that the administration of purified adrenocorticotropic hormone (ACTH) or the subjection of the animal to stress, produces a decrease of ascorbic acid in the adrenal cortex within an hour, and the amount of decrease is proportional to the dose of ACTH or the degree of stress to which the animal has been subjected. If the anterior pituitary has been removed there is no change in the adrenal ascorbic acid in response to stress. Administration of adrenal cortical hormone (ACH) prevents the decrease in adrenal ascorbic acid which ordinarily accompanies the exposure to stress, but it does not prevent the decrease which results from the injection of ACTH. It may be inferred, therefore, that the presence of ACH in the circulation inhibits the release of ACTH. They have shown that the degree of inhibition of ACTH activity is proportional to the amount of administered ACH and, also, that the greater the degree of stress to which the animal is subjected, the greater is the amount of ACH required to inhibit ACTH activity. The inhibiting power of five crystalline adrenal steroids has

been estimated. If a potency rating of 4 is arbitrarily assigned to 17-hydroxycorticosterone, the rating of 17-hydroxy-11-dehydrocorticosterone is 4, corticosterone 1, desoxycorticosterone 1/2 and progesterone 1/50.

Carpenter, MacLeod & Reiss (51) have studied the effect of ACTH on the respiratory metabolism of the adrenal cortex of the rat. Oxygen consumption was measured by the direct method of Warburg. The lactic acid produced aerobically was also measured. Twenty-four hours after giving rats a massive dose of ACTH the adrenal cortex showed an oxygen uptake approximately 25 per cent higher than that of the controls. The aerobic glycolysis was variable but tended to be higher in the treated group. The water content of the adrenals increased during the first hours after treatment but subsequently decreased. The nitrogen content of the dry substance showed a tendency to rise continuously after treatment.

Adrenal cortex and lymphocyte response.—Elmadjian, Freeman & Pincus (81) have shown that the administration of glucose (1.0 cc. of 50 per cent solution, orally) causes a prompt lymphocytopenia in the normal rat but not in the adrenalectomized rat. This finding supports Abelin's (2) earlier observation that the feeding of carbohydrate lowers the cholesterol content of the adrenal. Freeman & Elmadjian (92) have correlated the blood sugar and the absolute lymphocyte level of normal persons subjected to a glucose tolerance test (Exton-Rose technique). It was found that the lymphocyte count shows a trend which is opposite to that of the blood sugar level. The lymphocytes are decreased in the thirty and sixty minute samples when the blood sugar levels are elevated, and subsequently they are increased as the blood sugar falls. The relationship of blood sugar level to adrenal cortical activity will be discussed further in connection with experimental diabetes.

Yoffey & Baxter (255) have described the regressive changes in lymph nodes and thymus of the rat resulting from the daily administration of ACTH for four weeks. Curiously enough, ACH administered to rats over a similar period of time caused slight but definite hyperplasia of the lymph nodes. An indirect action of x-radiation on lymphocytes mediated via the pituitary-adrenal cortical mechanism has been demonstrated by Dougherty & White (76). They found that small doses of x-radiation, such as 10 r, produced lymphopenia, tissue lymphocyte degeneration, and increase in total serum protein and gamma globulin in normal mice

but not in adrenalectomized mice. Doses of 200 r produced these same changes in adrenalectomized as well as normal mice. Therefore x-rays produce both a direct and indirect effect on lymphocytes. This would explain the humoral mechanism which has been demonstrated by Barnes & Furth (20) in which radiation of one of a pair of parabiotic mice, the other being shielded, caused extensive lymphoid tissue changes and lymphopenia in both mice. A valuable monograph entitled *Studies on Thymolymphatic System* has been published by Andreasen (14). This worker has shown, in a recent study, a sex difference in the size of lymph nodes and spleen in young mature guinea pigs, both lymph nodes and spleen being larger in females (15).

Adrenal insufficiency.—Ingle & Oberle (125) have shown that salt-treated adrenalectomized rats excrete the same amount of urinary nonprotein nitrogen as sham-adrenalectomized animals during a twenty day postoperative period of forced feeding and during ten days of fasting. They conclude that the adrenal cortex is not essential in the catabolism of protein or in the ability of the animal to mobilize its own tissue proteins during fasting. It should be pointed out, however, that without the additional sodium chloride the adrenal cortex or its equivalent in steroid hormones would be essential in these mechanisms [Anderson (10)]. Salt partially restores altered function caused by removal of the adrenal cortex, while adrenal cortical hormone carries this restoration to completion. An understanding of the mechanism by which sodium chloride helps to restore the disabilities in the adrenalectomized animal might help toward an understanding of adrenal cortical function. Ingle *et al.* (127) have studied, also, the relationship of the adrenal cortex to changes in urinary nonprotein nitrogen following multiple fractures. Their results show that the increased nitrogen excretion which normally develops following fractures may require the presence of adrenal cortical hormone, but it is not caused specifically by the increase in secretion of hormone which occurs during stress. Leathem (143) has shown that adrenalectomized rats maintained on sodium chloride for twenty days have a subnormal plasma albumin concentration, but that pair-fed control rats exhibit the same low plasma protein concentration and the same impaired growth rate. Gonzales & Angerer (101), found that adrenalectomy in rats caused a decrease of 73 per cent in the oxygen comsumption of red blood cells. This was obtained at the

end of the second postoperative day and remained thus until the terminal stage. This defect did not occur if the rats were treated with either sodium chloride in the drinking water, or given desoxycorticosterone acetate (DOCA) or ACH. Jaudon (129, 130) has reported an interesting case of Addison's disease developing in a six-month-old infant who has been well controlled with DOCA for over two years.

The changes in skeletal muscle following adrenalectomy have been determined by Conway & Hingerty (55). Potassium, magnesium, phosphocreatine and glucose-l-phosphate were increased, whereas sodium, glucose-6-phosphate and fructose-l-6-diphosphate were decreased. Plasma constituents for the same rats showed an increase of potassium, magnesium, urea, total phosphate, and inorganic phosphate, and a decrease in sodium, chloride, carbonate and calcium.

Water diuresis tests in the diagnosis of adrenal insufficiency have been reviewed by Gaunt (98) and by Levy, Power & Kepler (149). Individuals with adrenal insufficiency apparently lack the capacity to excrete at a normal rate water which has been ingested or given intravenously. The mechanism of the disturbance is not understood; there is the possibility that both the distribution of water in the body and the altered renal function may be involved.

Physiologic properties of adrenal steroids.—Ingle and associates (126) have compared the acute effects of corticosterone and 17-hydroxycorticosterone on body weight and urinary excretion of sodium, potassium, chloride, nitrogen and glucose on normal rats which were force-fed a high carbohydrate diet. Glycosuria with hyperglycemia was induced in four of the five rats given 5 mg. of 17-hydroxycorticosterone daily, and in two of the five rats receiving 5 mg. of corticosterone daily. At this dose level both compounds caused an increase in the excretion of sodium, potassium, chloride, and nitrogen, and also inhibited weight gain, but 17-hydroxycorticosterone caused the greater response. With this amount of hormone in each case it appears that the differences in biologic properties are quantitative rather than qualitative. In smaller doses (1.0 and 0.5 mg.) corticosterone caused some retention of sodium; 17-hydroxycorticosterone has never been reported to cause sodium retention at any dose level. The question is raised whether in this respect it differs qualitatively from corticosterone or whether the apparent difference is a matter of relative potency

and dosage. Is the sodium diuresis which follows the administration of 17-hydroxycorticosterone a physiologic property of this hormone or is it a nonspecific response to a sudden metabolic upset? The answer is still lacking. When ACTH was tested under similar conditions in amounts of 7 mg. daily, it produced changes similar to those produced by 17-hydroxycorticosterone except for less consistent changes in urinary sodium and chloride [Ingle, Li & Evans (123)]. Thatcher & Hartman (227) have prepared a substance from the adrenal which is highly potent in its capacity to cause retention of sodium, but has no effect on potassium excretion or gluconeogenesis.

The metabolic effects of 11-dehydrocorticosterone (compound A) have been observed in patients with adrenal insufficiency (89, 183). Its effect on sodium retention is far less than that of DOCA. The effects on urinary nitrogen, potassium and inorganic phosphate are not constant, although in general there is an increased excretion of these metabolites. Very little influence upon the glucose tolerance curve was noted. Derman (70) has shown that DOCA (2 to 5 mg. daily) increases the glycosuria in phlorhidzin-treated rats. This could be demonstrated both in normal and in adrenalectomized rats. Bruzzone, Borel & Schwarz (43) have shown that acetoxypregnenolone will maintain adrenalectomized guinea pigs for periods of four to five months as well as DOCA but the amounts required are virtually six times that of DOCA. Emery (82) found that DOCA can be substituted for progesterone in bringing about relaxation of the pubic symphysis in oophorectomized guinea pigs.

Relation of adrenal cortex to kidney.—From a study of the effects of various endocrine influences upon renal function on the dog reported by White, Heinbecker & Rolf it would seem that it is the adrenal cortex which is most important for normal renal function. In this communication the authors have summarized their previously published work on diodrast (D) and inulin plasma clearances and on maximum tubular excretion of diodrast (D Tm) in hypophysectomized dogs, and to this they have added studies on dogs after removal of thyroid, ovaries or adrenals. The effects of various hormones have also been observed. Their observations are as follows: Within a few days after hypophysectomy both D clearance and inulin clearance drop 50 to 60 per cent of normal and remain at that low level. The fall in D clearance is not due to a

drop in renal extraction of D, for this remains normal. D Tm drops within a few days to 50 per cent of normal, with a further decline to 20 or 30 per cent of normal within a few weeks, where it remains permanently. Thyroidectomy produces a fall in D clearance and D Tm but little or no effect on inulin clearance; all these effects are far less than after hypophysectomy. Administration of APE, which results in large increases in D and inulin clearances and in D Tm in normal and hypophysectomized dogs, produces small and inconsistent rises in the thyroidectomized dog. Ovariectomy does not affect any of these functions. Dogs which have been kept on suboptimal amounts of ACH after adrenalectomy so that they show only mild adrenal insufficiency and have normal values for blood volume and for plasma nonprotein nitrogen, sodium, and potasium, still show a very marked fall in D clearance and in D Tm but less of a fall in inulin clearance. These values are restored to normal when adequate amounts of DOCA are given to the adrenalectomized dog, but they are not affected by APE administration. From these observations it would seem that it is the loss of ACTH rather than either gonadotropic or thyrotropic hormones which is responsible for the impairment of renal function after hypophysectomy. The authors leave enough room open, however, to include the possibility that there is another renotropic hormone of the pituitary besides ACTH. Page, Ogden & Anderson (178) showed that hypophysectomy causes a fall of blood pressure in rats with renal hypertension and that DOCA, 2 mg. daily, restores the hypertension but not quite to the high level present before hypophysectomy. Simpson, Li & Evans (221) failed to show any renotropic effects in rats on the administration of ACTH; however, their test for the renotropic effect was based on changes in weight of kidneys rather than on restoration of renal function in hypophysectomized animals. Hay (111) has demonstrated a renotropic effect, based on kidney weights, from anterior pituitary extract (APE) in thyroidectomized rats; however, the presence of the thyroid augmented the renotropic effect. Mårtens & Nylén (164) and Nylén (176) have confirmed the observation of Selye (215) that DOCA causes a statistically significant kidney hypertrophy in female mice, but they were unable to show that it had any effect on the compensatory hypertrophy of the remaining kidney after unilateral nephrectomy in the same test animal. DOCA

did not cause renal hypertrophy in male mice of the same strain. Nylén (177) was unable to confirm Selye's (216) finding that DOCA prolongs the survival of nephrectomized female mice.

Hall *et al.* (106) have reported additional observations on the production of nephrosclerosis and cardiac lesions as a result of administration of lyophilized anterior pituitary material to rats which have been unilaterally nephrectomized and given 1 per cent sodium chloride to drink. Adrenalectomy prevented the nephrosclerosis, even when cortin was administered in addition to the pituitary extract. Knowlton and co-workers (139) were not successful in producing nephrosclerosis with DOCA and sodium chloride such as Selye (217) has reported, but they have shown that DOCA in doses of 2.5 mg. daily together with a high salt intake (1.5 per cent sodium chloride in diet) is capable of producing striking anatomical and physiological disturbances in rats. Normal rats show hypertrophy of heart and kidneys but no hypertension. In animals rendered nephritic by means of a rabbit anti-rat-kidney serum, not only are the same changes observed, but in addition, the severity of the nephritic process is greatly increased by DOCA and sodium chloride, and the animals develop hypertension. These effects are abolished, or at least reduced, if the rats are fed a diet which is virtually sodium-free. The suggestion is made that the toxic effects of DOCA may possibly be the result of sodium "poisoning." In this connection one might call attention to another observation, namely that of Perera & Blood (182) that hypertensive patients do not show an increased urine volume following rigid withdrawal of sodium chloride for twenty-four hours such as is manifested in normal individuals. It has been suggested that this difference in response may be referable to changes in the kidney mediated by the adrenal cortex.

Urinary excretion of adrenal metabolites.—Venning & Kazmin (237) and Talbot *et al.* (223) have studied the urinary excretion of 11-oxycorticosteroid-like substances (also referred to as corticoids or glycogenic corticoids) in normal individuals. Venning & Browne (236) and Talbot *et al.* (223) have assayed these substances and the 17-ketosteroids in the urine of patients with various endocrine disturbances.

Forbes and associates (88) have reported the 17-ketosteroid excretion of sixty-six persons who were followed through some sort of medical or surgical injury. In normal individuals the excretion

usually rises for a brief period (one to three days) and falls until convalescence is achieved, when it returns to normal. In debilitated individuals the initial level is subnormal and the response to injury usually small or absent. In contrast to this it has been shown by Davison, Koets & Kuzell (66) that patients suffering from ankylosing spondylarthritis have an elevated urinary 17-ketosteroid content. This is a condition which occurs chiefly in males. It was found that thirteen patients with this condition, all males, excreted an average of 27 mg. 17-ketosteroids per day, which is significantly high as compared with an average of 14 mg. for normal males.

Islets of Langerhans and Experimental Diabetes

Several reports on the problems of carbohydrate, fat and protein metabolism, and experimental diabetes have been published. Some of them will be referred to under special headings in this review. Those of general interest to which attention is called are: Riddle and his associates, *Studies on Carbohydrate and Fat Metabolism with Especial Reference to the Pigeon* (199); Samuels, *The Relation of Anterior Pituitary Hormones to Nutrition* (208); Young, *Experimental Diabetes* (257); Abelin, *Die Bedeutung der Nebennierenrindenhormone und der Steroide für den Kohlenhydratstoffwechsel* (4); and Houssay, *The Thyroid and Diabetes* (117).

Alloxan and diabetes.—Houssay, Brignone & Mazzocco (118) have reviewed the effects of alloxan in the dog, Jarrett (128) alloxan diabetes in sheep, and Gaarenstroom (95) and Lazarow & Palay (142) the production and course of alloxan diabetes in the rat, the latter emphasizing the importance of the intravenous route of administration of the drug. In all three species the intravenous administration of alloxan was followed by the same triphasic response of the blood sugar level—an initial hyperglycemia followed by a transient hypoglycemia and finally permanent hyperglycemia. Shipley & Beyer (218) noted a brief hypoglycemia followed by a temporary hyperglycemia, then a prolonged second hypoglycemic phase, and finally permanent hyperglycemia, in fasted dogs injected with alloxan. Cutting the vagus delayed the onset of the second hypoglycemic phase. Covian (57, 58) has made extensive studies on the physiologic aspects of alloxan diabetes. Unfortunately his work has not been available to the reviewer.

Cutting & Laqueur (63) have described the cellular changes in the pancreas of the rat during the forty-hours immediately following the administration of alloxan. The Golgi apparatus in the beta cells appear to be "progressively altered toward disintegration" during the first twenty-four hours. Di Pietro & Cardeza (184, 185) have described alterations in the dog's kidney limited to the tubular epithelium and massive fatty degeneration and necrosis in the liver. In the first eight days after the giving of alloxan, the dog's pancreas shows degranulation of the beta cells, nuclear pycnosis and hydropic degeneration. After the second week there is a preponderance of alpha cells over beta cells. In the chronic cases (up to 249 days) hypertrophy of the islets and hyperplasia of the alpha cells are noted. Duff, McMillan & Wilson (78) have arrived at a similar conclusion that the alpha cells are increased in diabetic rabbits which have survived several months after alloxan injection. They have demonstrated hydropic degeneration in the pancreatic ductules and islets in the rabbits with longstanding, severe diabetes. These hydropic cells are probably not altered beta cells, but rather, indifferent cells of the islets which persist for many months without showing evidence of disintegration. The hydropic change is reversible if the animals are treated with adequate doses of insulin. The reversed islet cells in the treated rabbits appear to be unduly numerous, suggesting proliferation. The islets are made up, in part, of indifferent nongranular cells and, in part, of cells exhibiting varying degrees of granularity of the beta type. Those with a full complement of granular cytoplasm are indistinguishable from the beta cells of normal islets. As a result of a comparative study of groups of rats treated for long periods with small doses of alloxan, Hughes (120) has concluded that in the normal cycle of formation, growth, maturation and destruction of islet cells, acinar cells of the pancreas develop into beta cells of the islets. Hughes has called attention to the observation that many acinar cells persist after ligation of the pancreatic duct. It is suggested that these acinar cells may be destined to become islet cells and therefore are not affected by the ligation. A remarkable finding which suggests a relationship between the acinar tissue and the islet cells is that of Walpole & Innis (240), who have shown that after ligation of the pancreatic duct in the rabbit with resulting sclerosis of the acinar tissue but with no effect upon islet tissue,

the administration of alloxan has no pathological effect upon the islet tissue and does not produce diabetes.

Herbut, Watson & Perkins (113) have produced diabetes and portal cirrhosis in rabbits with alloxan. Menten & Janouch (170) have correlated the degenerative changes in the convoluted tubules of the kidney following alloxan administration in the rat, with a depletion of renal alkaline phosphatase. This has been demonstrated by chemical and histochemical techniques. Burgen & Lorch (44) have shown alloxan and three other diabetogenic ureides to be strong inhibitors of alkaline phosphatase in the concentrations which are required to produce diabetes. This is quite independent of the power of alloxan in concentrated solutions to deaminate and decarboxylate amino acids. A number of alloxan homologues have been shown to be diabetogenic, such as N-methyl, ethyl and propylalloxan, alloxantin, dimethylalloxantin, diethylalloxantin, and dialuric and methyldialuric acids [Brückmann & Wertheimer (42)]. Cutting & Laqueur (63) have shown that colchicine administered simultaneously with alloxan to rats, inhibits the second hyperglycemic phase and also inhibits the increase in blood uric acid which appears at about forty-eight hours after alloxan injection. Levey & Suter (148) have demonstrated that ascorbic acid given one minute before the alloxan injection to rats, increases the diabetogenic effect of alloxan. The diabetogenic effect of alloxan is prevented by the simultaneous injection of sulfyhydryl compounds such as glutathione, cysteine [Palay & Lazarow (179)], and BAL, which is 2, 3-dithiopropanol [Tislow & Chesler (231)]. The mechanism by which alloxan damages the beta cells is obscure. The difficulty lies in the fact that an understanding of the biochemical processes in the islet cells is lacking.

Pituitary and diabetes.—The present status of our knowledge of the relation of the anterior pituitary to experimental diabetes is well summed up in a review by Lukens (152). No single purified pituitary hormone contains all the diabetogenic properties of crude anterior pituitary extract. Growth hormone is ketogenic and, by the present limited criteria, inhibits the utilization of carbohydrate. ACTH mobilizes protein and carbohydrate and therefore is necessary for the gluconeogenesis observed in diabetes. The mechanism of action of APE is still poorly understood; however, there is evidence that it induces suppression of carbohydrate utilization and

over-production of glucose, and that protein and carbohydrate food are necessary for the greatest diabetogenic effect. The anterior pituitary is a factor in maintaining an organism during fasting, and for this purpose it achieves a "fairly definite quality and quantity of a metabolic mixture." The administration of APE to fasted animals adds little to the effect of starvation and does not produce diabetes. To the fed animal, e.g., the dog, these extracts readily produce diabetes. Supposedly the APE sets the metabolic pattern for fasting so that the protein and carbohydrate which are fed, are in excess of what can be utilized and therefore are excreted as glucose. If the hyperglycemia is sustained long enough, at least in the dog and cat, the islets of Langerhans undergo a sequence of hydropic degeneration and finally atrophy, which results in a permanent diabetes. Partial pancreatectomy and APE extract have caused lesions of the pancreas, but only in the presence of sustained hyperglycemia.

Dohan & Lukens (74) have shown that prolonged intraperitoneal injections of massive doses of glucose to cats causes sustained hyperglycemia and finally produces hydropic degeneration of the islets and a permanent diabetes. Anderson & Long (12), using a technique of perfusion of the isolated pancreas, have shown that hyperglycemia stimulates the islets directly to produce insulin. With the same technique they have shown (13) that APE does not stimulate the pancreas directly to secrete insulin, that is to say, it does not possess any pancreatropic action. Growth hormone, thyroxin and adrenocortical hormone have no stimulating effect upon the islet cells. On the other hand, APE and growth hormone inhibit the secretion of insulin which would ordinarily occur in response to hyperglycemia. This inhibitory action may be a part of the mechanism which is responsible for the degenerative changes in the islet cells resulting from APE administration. Lukens (152) has emphasized the fact that the hydropic degeneration seen in experimental diabetes can only occur in the presence of hyperglycemia. To this, should be added that in all of the cases of permanent experimental diabetes the anterior pituitary hormones have been present, supplied by parenteral injection or by the animal's own pituitary. From the work of Abelin (2) and Elmadjian *et al.* (81) there is evidence that administration of glucose stimulates the pituitary to secrete ACTH. Can it be that in the experiments of Dohan & Lukens (74)

the excessive glucose administration had a stimulating effect upon the pituitary? To answer this question an attempt should be made to produce diabetes by excessive glucose in hypophysectomized animals. Shipley & Meyer (219) have shown that when a diabetic and a normal rat are united by parabiosis, the pancreas of the normal rat supplies insulin to the diabetic, but not enough to bring its blood sugar to normal. This additional work on the part of the pancreas does not leave any evidence of exhaustion or hyperfunction of this gland after surgical separation of the parabionts.

Houssay and his students (119) have reaffirmed their earlier claims that pituitary diabetes can be produced in the absence of the adrenal cortex. In their most recent series they have shown that in dogs with partial pancreatectomy the injection of APE produces pituitary diabetes: (*a*) in fourteen animals with unilateral adrenalectomy, (*b*) in six animals with total adrenalectomy kept alive with DOCA, and (*c*) in four animals with total adrenalectomy kept alive with sodium chloride only.

The effect of insulin on the fat-mobilizing action of APE has been studied by Campbell (50). In fasted guinea pigs, rats and mice, insulin lessens the rise in liver fat which ordinarily occurs in response to APE administration. In the opinion of this investigator the insulin may act by stimulating the utilization of small carbohydrate reserves in the fasted animal or by increasing the efficiency of utilization of carbohydrate formed by gluconeogenesis, and thus it decreases the fat mobilization which occurs in response to APE.

Adrenal cortex and carbohydrate metabolism.—Abelin (2, 3) was the first to show that seven to eight hours after feeding a carbohydrate meal (glucose, sucrose, galactose or fructose) to rats which had been fasted sixteen to eighteen hours, a reduction of about 25 per cent in the adrenal cholesterol occurs. The fall in adrenal cholesterol is correlated with the increase in liver glycogen. Feeding a diet high in carbohydrate in which the fat content consists of 10 per cent vegetable oil, doubles the adrenal cholesterol. A carbohydrate meal augments the fall in adrenal cholesterol which occurs in response to APE (5). Abelin (4) has suggested that the rise in blood sugar from the glucose meal may stimulate the pituitary to secrete ACTH, which causes the release of ACH and this, in turn, facilitates the building of liver glycogen. Ingle (122) found that rats which died because of over-feeding of a high carbohy-

drate diet showed hypertrophy of the adrenal cortices. Foglia (86) and Bennett & Koneff (28) have noted hypertrophy of the adrenals in rats with sustained hyperglycemia.

Insulin.—The action of insulin has been reviewed by Bouckaert & de Duve (34), and the chemistry and physiology of insulin by Jensen (131) . Ingle & Nezamis (124) have studied the effect of insulin on the tolerance of normal rats to the overfeeding of a high carbohydrate diet. It was found that insulin did not delay the onset of glycosuria but it did permit the animals to tolerate larger amounts of carbohydrate before they were killed by overfeeding. Frame & Russell (91) have explored the problem of effects of insulin and APE on blood amino nitrogen in eviscerated rats. Insulin together with glucose depresses the rise in blood amino nitrogen after evisceration; APE and glucose do not. However, APE seems to intensify the action of insulin in depressing the rise in amino nitrogen It has been shown in studies on mental patients that insulin hypoglycemia produces a marked fall of the blood amino acids (109), Crandall & Lipscomb (61), using the angiostomy technique of London, have measured directly the hepatic glucose production in experimental diabetes The evidence suggests that over-production of glucose by the liver is not a significant factor in diabetes.

Attention is called to several clinical reports which contribute to the study of the action of insulin: Darnaud (65) has prepared an interesting review of the problem of insulin resistance in patients; McGavack *et al.* (159) have reported a case of mild diabetes with recurring attacks of extreme insulin resistance; Luft (154) and Zondek *et al.* (258) have reported cases of hyperinsulinism; and Wilder (246) has described a case of pancreo-pituitary hypoglycemia.

Diabetes and nutrition.—Gaebler & Mathies (96) have shown that the water-soluble vitamins required by the intact dog may influence nitrogen equilibrium in the depancreatized dog. Pantothenic acid and pyridoxin seem to have some influence in the control of glycosuria.There is no evidence that the human diabetic has difficulty in the normal conversion of carotene to vitamin A [Kimble and co-workers (138)]. Schneider, Lewis & McCullagh (213) have found that the plasma proteins of patients with diabetic retinitis are characterized by low albumin, high beta globulin, and a virtually normal total protein value. The retinitis improved with a high protein diet.

Anterior Pituitary

In this chapter on the metabollic aspects of the endocrine glands there has been an attempt at decentralization of pituitary function. It will be noted that the thyrotropic and adrenocorticotropic hormones have been discussed in connection with their respective target glands,the gonadotropic and lactogenic hormones have been handled in the chapter on reproduction, and the diabetogenic properties of anterior pituitary extracts and growth hormone have been considered under the islets of Langerhans and experimental diabetes. This leaves only the general aspects of the anterior pituitary to be treated in this section.

Anatomy.—Hartman, Fain & Wolfe (110) have re-examined the evidence of a fourth cell type in the anterior pituitary of the dog. They feel that it is not a variant of either the usual basophil or acidophil and have termed it the erythrosin cell. This fourth cell type is, apparently, the same as the carminophil described by Dawson (67) in a monograph on the specific secretory activity of the anterior pituitary of the cat. Dawson has suggested that the carminophil cell may possibly secrete lactogenic hormone. Payne (181) has described the cellular changes in the anterior pituitary of the white Leghorn fowl from embryo to old age. Rasmussen (194) has made a quantitative analysis of growth of the human pituitary from birth to the age of twenty. The weight of the whole gland (without capsule or stalk) plotted against age shows a straight line relationship. There is a sex difference, the anterior lobe of girls being larger than that of boys. Wrete (253) found, when weighing certain endocrine organs from male white mice a month after unilateral nephrectomy (*a*) that the pituitary had undergone a statistically significant increase in weight; (*b*) that the thyroid was probably also increased in weight and (*c*) that the total dry substance weight of the adrenals had probably undergone a decrease. Anthun (16) has shown that the anterior pituitary of normal rabbits and rats is not influenced by large doses of roentgen irradiation (e.g., 1300 r), as judged by pituitary weight and histological evidence. Evidently normal pituitary tissue is much more resistant to irradiation than overactive pituitary tissue. Luft (153) has reported success in depressing the adrenocorticotropic activity of the pituitary in patients with Cushing's disease.

Chemistry and physiology.—An excellent review on the prepara-

tion and chemistry of the hormones of the anterior pituitary has been prepared by White (244). Friedgood (94) has published a monograph on the endocrine function of the hypophysis. Weitze (241) has succeeded in establishing parabiosis between hypophysectomized mice and normal mice. It has been shown that one normal pituitary is not sufficient for the normal development of two mice; however, if parabiosis is established between a dwarf mouse (hereditary anterior pituitary dwarfism) and a normal mouse, the normal pituitary supplies enough of the pituitary hormones to enable the dwarf to grow.

The very difficult problem of evaluating the physiologic findings in animals with varying degrees of hypophysectomy has been discussed by Keller, Lawrence & Blair (136) in a detailed account of their experiences with hypophysectomized dogs. It was their impression that some of their animals in which only a very minute fragment of hypophysial tissue was left but in which all of the stalk and part of the tuber cinereum were removed, showed no deficit in carbohydrate metabolism or in adrenal function. They make bold in suggesting that "there are elaborated in the immediate environs of the hypothalamus endocrine principles having actions contrary to the actions of certain of the known hypophysial principles."

Anterior pituitary and hypothalamus.—No attempt will be made to review hypophysial-diencephalic relationships, but attention is called to several important studies which directly concern endocrine physiology. Borell, Westman & Örstrom (33) have studied the phosphate turnover in the pituitary, tuber cinereum and ovaries using radio phosphorus as an index of functional activity after coitus in the rabbit. Brooks and his students (37 to 41) have contributed a series of papers on the problem of hypothalamic obesity, and Brobeck (35) has reviewed the mechanism of the development of obesity in animals with hypothalamic lesion. Brolin (36) has made an extensive study of the structural and hormonal reactions of the anterior pituitary of rats exposed to cold. He presents good evidence to support the conclusion that the thyrotropic function of the pituitary is dependent upon the stalk connection with the hypothalamus. Sunderman & Haymaker (222) have reported a case of hypothermia and elevated blood magnesium in a child with a hypothalamic lesion. A review on the influence of the nervous system upon the pituitary has been prepared by Houssay (115).

In discussing the subject of polyostotic fibrous dysplasia (Albright's syndrome), Albright (9) has called attention to the evidence that the precocious sexual development in this type of clinical case is mediated through the hypothalamus. Luft & Müller (155) have reported the occurrence of various endocrine disorders occurring in poliomyelitis.

Parathyroid

A new method of preparing parathyroid hormone which gives a higher yield than the methods used heretofore has been developed by L'Heureux, Tepperman & Wilhelmi (147). The method consists of preparation at low temperatures of a fat-free gland powder, then gentle extraction with dilute hydrochloric acid and finally fractionation of this extract with acid and neutral acetone. The preparation is a light brown amorphous powder with a potency of 200 to 300 USP units per mg. Electrophoresis shows it to be heterogeneous, containing at least two components; ultracentrifugal analysis shows that no substance of high molecular weight is present. Salomon, Gabrio & Smith (206) have described a new method for quantitative determination of calcium in blood. The procedure consists of the preliminary treatment of the plasma (0.5 ml.) by ashing with a perchloric acid-nitric acid mixture, the precipitation of calcium as calcium oxalate, and the titration of the oxalate ion with ammonium hexanitratocerate in perchloric acid solution using nitro-*o*-phenanthroline ferrous sulfate as indicator.

The effect of prolonged treatment with parathyroid hormone on the composition of the bones of puppies with varying calcium intakes has been studied by Burns & Henderson (46). They found that the amount of calcium laid down in the bones varied with the calcium intake and that the parathyroid hormone injections had no effect on bone growth and calcification. At a fairly steady level of calcium intake and a steady increase of the hormone injected, disorganization of bone did not occur. The increased excretion of calcium, which follows injection of parathyroid hormone, is not maintained except on a diet which itself gives a negative calcium balance. Under regular conditions of diet and hormone injections, the parathyroid hormone merely increases the rate of bone resorption and repair without influencing the chemical composition of the bone laid down. The influence of estrogens on calcium metabolism and bone has been studied by Pindborg (187), Silberberg &

Silberberg (220), Salomon *et al.* (205), and Baker & Leek (19). The problem of tetany has been discussed by Hadorn (105).

Mandl (166) has published an excellent review of hyperparathyroidism. Norris (175) has analyzed all cases of parathyroid adenoma published since 1903. There have been several reports of cases of hyperparathyroidism (30, 45, 174, 200, 209). Mellgren & Lundh (169) and Wilton (248) have noted changes in the anterior pituitary in their cases of hyperparathyroidism and have suggested a relationship between the pituitary and the parathyroid glands.

Assay of Hormones

Thayer (228) has contributed a chapter on *Methods of Biossay of Animal Hormones* in Volume IV of *Vitamins and Hormones*. White (244) has included assay methods in a review of the anterior pituitary hormones. A valuable discussion of the application of the principles of statistical analysis to bioassay of hormones has been prepared by Pugsley (188).

In the past year a good deal of work has been done on the correlation of the urinary excretion of adrenal steroids, particularly the steroids which have glycogenic activity, and various clinical conditions. Methods of bioassay of these 11-oxycorticosteroid-like substances have been published by Venning, Kazmin & Bell (238), Dorfman Ross & Shipley (75), and Eggleston, Johnston & Dobriner (80). Colorimetric methods which supposedly assay the same substance have been described by Talbot *et al.* (224) and by Heard & Sobel (112). A clinical method for the chromatographic-colorimetric determination of 17-ketosteroids has been described by Dingemanse, Huis in't Veld & deLaat (72). By this method it is possible to determine the different 17-ketosteroids, including dehydro-iso-androsterone and androsterone quantitatively in a single specimen of 500 cc. urine. A method for the assay of ACTH based on the change in ascorbic acid level in the adrenal has been devised by Sayers & Sayers (212).

Lacey (140) has elaborated further upon the cross-over method of insulin assay in rabbits. Improvements in the method of detecting hypoglycemic reactions in the mouse assay for insulin have been suggested by Thompson (229) and by Young & Lewis (256). A method for the assay of insulin in blood which measures the insulin in terms of milli-units has been described by Anderson,

Lindner & Sutton (11). Tepperman, L'Heureux & Wilhelmi (226) have suggested a new method for assay of parathyroid hormone, using the change in the serum inorganic phosphorus of the rat as the measurement of activity. Welti & Roth (242) have used the metamorphosis of amphibians in measuring thyroid hormone activity of goitrous tissue. Curtis, Umberger & Knudsen (62) have prepared a graph and monograph for the statistical evaluation of the results of estrogenic assays.

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HEAT AND COLD[1]

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Introduction

The necessities of long-range and broad-scale attacks on . . . the relation between man and his environment were revealed under the stress of war. The value of coordinated attacks and of multi-directional approaches have been demonstrated, even by the small efforts made. Both physiology (including biochemistry) and psychology must be brought into action in cooperation. Other disciplines would undoubtedly be involved; these would include geographical climatology and sociology. Medical, economic, military, political and fundamental biological issues are involved (1).

This statement, which marked the formal recognition of human climatology as a field of science, is even more true when applied to the whole range of vertebrates, i.e., in the field of comparative vertebrate climatology. It is indeed gratifying that material permits this early post-war review to demonstrate that that "interdisciplinary research" (2) fostered by war needs is being carried forward in the pursuits of peace. Only one previous review (3) in this series has devoted a major subdivision to "comparative" studies. It is to be hoped that this can continue as a regular feature.

Human Reactions

While man is the subject of this section, reference will often be made to animal experiment by way of elucidation. A truly comparative section on Reactions of Birds and Mammals will follow.

Heat-regulating mechanisms.—Keller & Blair have developed an experimental technique (4, 5) of quantitative successive pontine section in cats which demonstrates (6) that heat-regulation is almost entirely controlled by fibres proceeding in the lateral parts of the reticular tissues directly from suprapontine regions, those controlling heat loss lying more laterally than those regulating heat production. The fibres travelling down in one side of the pons are apparently distributed bilaterally at some lower level, as the effects of pontine section, when present, were uniformly distributed.

[1] This review covers the period from July, 1946 to June, 1947.

Lower centres would seem to play a subservient role. Cortical area 13 appears to have some influence upon skin temperature, at least in monkeys (7).

Bernhard & Granit (8) have demonstrated that the cut end of a nerve is affected by temperature changes in two ways—cooling or marked heating renders the part electronegative, setting up a potential difference, while the innate tendency to a rhythmic variation of excitability varies with temperature in the usual fashion. The net result of the two processes dictates the production and character of the discharge. They advance the suggestion that this is the essential mechanism of thermosensory nerve endings, a concept which would accord with their general theory of sensory nerve-ending mechanisms. Differential responses to temperature of resting potential, action potential and conduction rate are linked to neurone theory by Bremer & Titeca (9). Wells (10) puts forward the concept that a thermal gradient, irrespective of direction, summates with other adequate stimuli for pain, thus explaining the usual relief obtained by superficially applied warmth.

Randall (11) finds that, whereas a local heat stimulus provokes sweating most readily in that part, a sufficiently strong one will evoke a bilateral response, and suggests spinal radiation as the mechanism. The importance of the reflex mechanism is shown by the fact that arterial occlusion diminishes but does not abolish this response.

Perkins (12) has shown by deafferenting limbs in experimental animals that the induction of shivering depends upon the integrity of afferent nerve fibres from the muscles in question, while the rate is determined by the natural physical frequency of the part. Spealman (13) finds a rectal temperature of 36°C. the critical point for the initiation of shivering. Adolph & Molnar (14) found the heat production by shivering to fluctuate ± 20 per cent. The maximal rate of heat production in their experiments was 210 kcal. per sq.m. per hr. for a $1\frac{1}{2}$ to 2 hr. exposure, and 147 kcal. per sq.m. per hr. for a 4 hr. exposure. Above these levels the muscles became fatigued. It is doubtful if there is any rise in the metabolic rate in response to cold apart from that due to shivering (15, 16).

The relationship between deep body temperature, cutaneous blood flow, thermal conductance and skin temperature receive further elaboration in a number of articles (14, 17, 18, 19) while the arteriovenous shunts provided by the "glomus" bodies are again

emphasized in applied literature (20, 21). When threatened with a fall in temperature, the first protective mechanism employed by the body is the reduction of superficial blood flow by vasoconstriction. The resulting shell of insulating tissue is more effective the greater the radius of curvature of the part. Thus the deep temperature of the trunk is better maintained than that of the extremities, and of a thick than a thin torso. Adolph & Molnar (14) found vasoconstriction to be maximal in resting nude man, in shade, at air temperatures of 70°F. Below this, once "storage" heat has been lost from the insulating shell, increased heat production is the only method of maintaining deep body temperature.

The blood flow through the hand varies, not only with the temperature of the hand, but also with the temperature of the body. Under comfortable body conditions Spealman (17) found blood flow least with moderately cold hands (15°C.) at 0.9 cc per 100 cc. tissue per min., but Forster *et al.* (18) obtained only 0.15 cc. at similar hand temperatures. At lower temperatures the flow increases again. Barcroft & Edholm (19) found the blood flow in the forearm to vary from 1.6 cc. per 100 cc. tissue per min. at 30°C. to 5.9 cc. at 37°C. They determined that a bath temperature at 34°C. was the equivalent of the clothed forearm at 18.5°C. air temperature. Here also, the temperature of other parts affected the rate of flow in the forearm, especially at the higher temperatures when local constriction was less. Kemp *et al.* (22), however, have shown that blood flow through the femoral artery may actually be decreased by heating the muscles of the hind limb.

Adolph (23) showed that it takes twenty minutes following exposure to heat for sweating to develop to a maximum. Randall (11, 24) by a simple but ingenious modification of the starch-iodide technique has demonstrated the details of sweat production. The basic activity of the glands is cyclic. As the temperature rises, the cycles become more frequent and the basal number of active glands is increased. Visceral and other sensations increase the activity. When all glands are active, further increases in sweating are due to increased output per gland. This second phase is of slower onset. The gland population of any skin area can be revealed by this method, using iontophoresis with mecholyl to insure maximal stimulation. Details of the composition of sweat are given in two articles (25, 26). Robinson (27) has shown that: (*a*) at a constant effective temperature of 25°C., rectal temperature and sweat loss

rise together with work while skin temperature remains constant; (*b*) with a constant level of work and effective temperature of 10 to 32.5°C., rectal temperature remains steady but skin temperature and sweat increase with environmental temperature; (*c*) with a constant level of work and effective temperature 32.5 to 35°C., rectal temperature rises as well.

Indian reports (28, 29) place the mean rectal temperature of normal persons in that region at 98.75°F. ±0.50, about 0.4°F. above English figures, with a range of 96.7 to 100.4°F. This "essential hyperthermia" tends to disappear with rest in bed for twenty-four hours. Fifty-five per cent of persons examined in India had a diurnal range of 1.6 to 2.6°F. Essential oral hyperthermia is reported as a neurosis in some patients after prolonged hospitalization (30). Attention is again directed to the relationship between basal body temperature and the menstrual cycle (31 to 34). The precooling of arterial blood in the extremities by contiguous veins has been directly demonstrated by Bazett (35), who passed thermocouples up his radial artery.

Consequential changes.—Man is supreme as a homeotherm, but at a price. Thermo-regulation involves many, if not all, other systems in complex fashion. Some of these may approach a crisis long before there is any intrinsically important degree of change in body temperature. This is particularly true in heat.

Adolph & Molnar in their report (14) of field observations on exposure to cold, which came very close to achieving the ideals of laboratory experiments, demonstrate that cardiovascular changes are explicable as modifications of the thermoregulatory vasoconstriction to the metabolic demands of shivering. In their experience cold diuresis is increased by lying down, is accompanied by a relatively high specific gravity (1009) which distinguishes it from that of true water diuresis, and is less in amount than that of the blood volume change. Discomfort in their subjects came mainly from muscle reflexes, pain was usually replaced by numbness and hyperaesthesia, and dullness passing on to a stuporous condition occurred if the discomfort was endured. They did not observe any of the basking in the cold described by Barcroft. Mimeographed reports (36, 37, 38), and a paper (39) from the U. S. Field Medical Research Laboratory summarize war-time studies of the general effects of cold on military personnel. Efficiency of the hands was readily and markedly affected. Cowles & Nelson (40)

suggest the trial of low temperature treatment in tetanus and other toxic disturbances. Maison & Haterius (41) describe three modes of cardiac failure in hypothermia: (*a*) ventricular fibrillation with respiration continuing; (*b*) sinus rhythm going on to standstill with respiration continuing; (*c*) atrial standstill with ventricular escape at rates of 3 to 6 per min., but with respiratory failure. Elevated serum magnesium and hypothermia have been described (42) in neoplastic invasion of the hypothalamus.

Decline of sweating ability in heat appears to be of three types: (*a*) acute failure under severe conditions; (*b*) subacute failure in people repeatedly subject to moderately severe conditions; and (*c*) chronic failure in persons subjected to heat for periods of months or years. Heat exhaustion or heat stroke, depending upon the circumstances, must follow any important failure of the sweating mechanism, and may be confused at first with neurosis (43). We seem to have no better explanation for the first type than the "fatigue" of the sweating mechanism postulated by Gerking & Robinson who described the condition (44). No more satisfactory explanation is available for the second, which is described (45) as being of temporary nature if the subjects are "nursed" through this phase. Sulzberger and co-workers (46, 47) have confirmed the findings of Allen & O'Brien (48, 49), that the anidrosis of the third type follows upon an epithelialization and blocking of the sweat-ducts and that this is often associated with the clinical condition of "prickly heat" and other "tropical dermatoses." The reviewer considers that the problems of tropical dermatosis alone demand a major development of cutaneous physiology, and that such an enquiry might furnish a scientific basis for the very unscientific current practice of dermatology. If careful control of hydration is maintained during physical pyretotherapy, Schwemlein (50) finds only minor changes in the electrocardiogram. By direct cooling of the endocardium, Byer *et al.* (51) altered the pattern of the electrocardiogram thus indicating the participation in it of subendocardial muscular activity. Hall *et al.* (52) observed a reduced amplitude of muscular contraction after application of moist heat to overlying skin and relate this to reflex arterial constriction (22). Fischer (53) finds some correlation between muscle strength and the weather.

History has been repeated in the attention drawn by war conditions to heat stroke. Mesopotamia has lived up to its reputation,

while at least 157 fatal cases of heat-stroke occurred in army camps in the U. S. A. (54, 55). Yet practically nothing was heard of heat stroke in the S.W.P.A., and it remains a rarity in Australia, except, perhaps, in the very young and the old or the infirm, in whom circulatory and other disturbances invite disaster. The American cases appeared to fall into two groups, those occurring after one to two weeks of exposure to heat and those developing after two to six months. Malamud *et al.* (54) found widespread necrosis in the cerebellum, cerebral cortex and thalamus, with replacement type gliosis, distinct from the spotty necrosis of anoxia, and due, they believe, to the direct effects of high body temperature. There was also widespread punctate haemorrhage, which they attribute to the terminal shock-like state. Wright *et al.* (56) ascribe the purpuric manifestations to liver damage. Some part of these manifestations in certain cases may be due to acute anhydraemia as described by Cameron *et al.* (57). Changes in the electrocardiogram of a nonfatal case are reported (58).

The war showed that men can live healthily and work better under natural tropical conditions than was generally believed, but that mental fatigue and psychological disturbance occur rather more easily unless care is taken to provide the necessary external stimuli and to remove avoidable psychological stress (59, 60, 61). Herein lies both an encouragement and a warning to tropical settlement. There is no reason to regard "tropical neurasthenia" as a special clinical entity (62). The incidence of miscellaneous disturbances such as amenorrhoea (63), acute enteritis (64), traveller's edema (65, 66), eclampsia (67) have been discussed.

Factors Modifying Human Reactions

Nutrition.—A sober review (61, 68, 69) of the nutritional aspects of tropical service indicates that there are no very special requirements, beyond the psychological importance (*vide supra*) of consumer presentation and a general proportionality between prevailing temperature and calorie requirements (70). Under cold conditions, on the other hand, evidence has been adduced for attention to the composition of the diet. The Chicago group (71, 72) have shown that, on a restricted ration, protein is the more economical nutrient in preserving body weight and in its specific dynamic action, which is 50 per cent greater than that of carbohydrate at normal temperatures and 76 per cent in the cold; but

that with free feeding a carbohydrate diet improves heat regulation and psychomotor performance. A high-fat diet may even be a little superior in this respect. Long's work (16), on the other hand, suggests that protein improves heat regulation at all times. Decreasing the interval between meals to two hours markedly improves psychomotor reactions with all types of diet and improves heat-regulation with a high-fat diet. On the other hand, excess doses of vitamins were found not to improve resistance to cold (73). For the composition of tropical foods Nicholls (74) or Platt (75) should be consulted.

Clothing.—The intense interest in the climatological implications of clothing engendered by the war is being continued. Service reviews (76) endeavour to coordinate the findings, while earlier service reports are appearing in regular publications (77, 78, 79). It would appear that fairly sound prediction can be made of the climatic performance of materials and assemblies whose physical characters are known, along the lines laid down in the National Research Council's "Clothing Test Methods" (80), but it is time that the English "tog" (0.1°C. per watt per sq. m.) and the Canadian-American "clo" (0.116°C. per kcal. per sq. m. per hr.) units were reconciled (1 clo = 1.545 togs.), or that physical units were exclusively employed. For hot humid climates, the basic equations need development to include a term for subclothing convection. Coastal dwellers would agree with Yaglou (81) that the per cent wetted area required to ensure removal of water vapour solely by diffusion through the material is much too great for comfort, and is reducible by convection through neck, sleeve and leg openings. Belding *et al.* have described very clearly (82) the complex processes maintaining the heat balance in arctic clothing with varying degrees of activity and environmental conditions. Wind-chill and the vapour-barrier principle occupy a major place in current considerations of arctic clothing. Some important technical papers have appeared (83, 84, 85), but there is an urgent need for a comprehensive but lucid exposition of the physiological and physical principles involved in clothing problems.

Housing.—The concentration of attention upon air conditioning has somewhat obscured the basic importance of building materials and design in the control of internal conditions, especially for hot climates. These aspects have been brought back into the field of enquiry as regards India by Thoburn (86), while the Commonwealth

Experimental Building Station (87, 88), C.S.I.R. Building Materials Research Section (89) and Department of Labour and National Service (90) have taken up the problem in Australia, in which country air conditioning is too expensive for widespread domestic use. Industrial requirements have been subjected to critical enquiry by ASHVE members in a series of articles. Apart from basic problems (91) and technical considerations, three major queries arise: (*a*) is an effective temperature of 78°F. too high for comfort (92, 93, 94)? (*b*) does a variation in humidity matter inside the comfort zone (95)? (*c*) is "leaving shock" a real or important entity (96, 97)? The limits of conditions in Australian textile mills which are both reasonably comfortable to the workers and suitable for industrial operations have been determined (98). An ASHVE report (99) that noise makes little difference to work performance in heat substantiates some war-time observations of the reviewer. The mathematics of heat exchange and distribution in aircraft are set out in a series of articles (100, 101, 102) and reports (103). Solar radiation, radiation to outer space, conductive loss, frictional heating, engine heating, compression heating in pressurized cabins, and metabolic rate of passengers make a complex problem, which is further complicated by the time factor. Naval problems are reviewed in a series of duplicated reports (104, 105, 106).

Acclimatization.—Adolph & Molnar (14) support those who find no acclimatization to cold, even as regards mental attitude; but Glickman *et al.* (73) report that after exposure to −20°F. subjects exhibited a smaller decrement than before in rectal temperature when exposed with little clothing to 60°F. The demonstration that rapid improvements in pulse and temperature reactions to heat occur with relatively few repeated exposures has produced the idea (107) that acclimatization is complete in 80 per cent of people in four to seven days. The reviewer's experience puts him in agreement with Marsh (108) that several months are required for full adaptation of temperate zone dwellers to tropical conditions. The slow phase of acclimatization may be one of conservation in heat production or of improved efficiency of skin circulation. Christensen (109), like the reviewer, commonly finds a decrease in sweat rates with long term exposure. Keeton (21) suggests increased numbers of glomus bodies. Acclimatization, like training, appears to be more effective if carried out at levels higher than those antici-

pated in practice (110). On the other hand, long continued exposure to excessive heat or to moderate heat under psychologically depressive conditions (111) may reduce efficiency. Little success has been achieved in devising prediction tests of tropical adaptability (23).

Miscellaneous.—Burch (112) finds sweating rates decreased in patients with congestive cardiac failure to as much as 27 to 47 per cent of normal. The symptoms suggest that the increased loss through the lungs (113) does not compensate for this.

Fuhrman (114) reviews the effect of body temperature on drug action. From a mass of detail the following relationships appear: (*a*) rate of absorption depends upon change in blood flow induced by temperature; (*b*) rate of action usually increases with temperature; (*c*) rate of detoxication usually increases with temperature; (*d*) drugs may in turn influence body temperature by action on thermoregulatory centres or on cutaneous blood flow; (*e*) rate of excretion may be affected. The net outcome will vary in both size and direction with the species, nature of drug, size of dose, mode of administration, presence and importance of compensating mechanisms, similarity or contrast between effects of drug and resultant body temperature change, and criteria of drug effect used.

Anaesthesia in the tropics (115, 116) and the effect of temperature upon dinitrophenol action (117, 118), iodide excretion (119), vasopressor amines (120) and duration of barbiturate anaesthesia (121), are dealt with in separate papers.

Tolerances.—Under cold conditions (14) acute discomfort, fatigue of shivering or hypothermic stupor terminates permissible exposure. Under hot conditions lowered mental initiative, psychomotor inefficiency, peripheral circulatory failure, hyperthermia or occasionally heat cramp limit more acute exposure, while psychological disturbance or secondary pathological development limits the more chronic. Schickele (55) has established a "heat death line" above which some cases of heat stroke are likely to occur in U.S.A., but such conditions were the rule in New Guinea without heat stroke. Molnar (122) plots survival time in cold water against temperature and finds a sharp inflection about 65°F. A simplified account of heat tolerance is given by Adolph (123). Shelley *et al.* (79) found the limiting wet bulb temperature (WBT) for men marching nude at 3 mph. to be 94°F. at a dry bulb temperature (DBT) of 95°F. This was lowered by 2°F. when the DBT

was raised to 120°F. and by 2 to 4°F. with the adoption of clothing. Robinson & Gerking (124) find 190 kcal. per sq.m. per hr. to be the maximum metabolic rate for the maintenance of equilibrium for six hours at a DBT of 32.6°C. and a WBT of 31.6°C. Caplan & Lindsay (125) report that Indian coolies continued drilling rock for three hours at a DBT of 121.1°F. and WBT of 93.1°F, though with a fall in production to 70 per cent; while at a DBT of 121.3°F. and a WBT of 94.9°F. they were able to work for two hours with relative efficiencies of 43 per cent in the first hour and 30 per cent in the second. There are other suggestions of the thermal superiority of darker races (126). A careful thermodynamic analysis of heat exchanges under these conditions would be interesting. Mackworth found the average performance of telegraphists (127), like that of heavy psychomotor performance (128), to deteriorate with effective temperatures (E.T.) above 83 to 87.5°. Exceptionally skilled telegraphists, however, retained their efficiency until an E.T. of 92°F. was exceeded. The reviewer's experience with trained and acclimatized subjects accords with the last finding. Mackworth found, however, that prolonged visual search (129) was best at an E.T. of 79°F., falling off both above and below this level.

Reactions of Birds and Mammals

Heat-regulating mechanisms.—Cowles (130) urges the use of the term "endotherm" in place of "warm blooded." Bachrach associates normal body temperature with ionic balance (131). Neurological studies have been mentioned above. French workers (132, 133) have shown that while the adrenal medulla and epinephrine have an important calorigenic action, especially in a cold environment, neither cortical extract nor desoxycorticosterone have any such effect. There is some evidence, however, for calorigenic hormonal influences other than thyroxine and epinephrine. Most animals relax when first exposed to warmth, though with varying effectiveness, but agitation usually results from an excessive rise in body temperature (134). Shivering characterizes the reactions of birds as well as of mammals to cold, but dwindles when the body temperature falls too low (135).

The posture adopted by animals in heat is species-characteristic and may play a critical part in heat tolerance (134). If one can judge by the pulse rate, adjustments of peripheral blood flow are

developed mainly by the effectively sweating mammals, with the exception of special mechanisms in the wings of bats (136). All classes of mammals except rodents have widely distributed sweat glands (137), but their efficiency for heat regulation varies enormously. European cattle sweat somewhat (138), sheep moderately well (139), horses profusely. Bandicoots from tropical districts tend to show better developed sweat glands than those from colder areas (137). Until the highest primates are reached, the glands are mainly apocrine and possibly less efficient. A possible inhibitory action of arrector pili muscles on sweat secretion is reported (140). The effect of anaesthesia upon cutaneous water-loss and body temperature of animals is reported (141, 142). Homeotherms fall into four classes as regards pulmonary heat regulation: (*a*) those limited anatomically (echidna, some birds); (*b*) those in which increased ventilation follows a rise in body temperature (most marsupials, birds, pig); (*c*) those in which it precedes a marked rise in body temperature (rabbit, dog, cat, cattle) (143, 144, 145); (*d*) those in which other regulatory mechanism make it relatively unimportant (man). Sheep (146) link the last two groups. Morphological features such as the pendulous tissues of Indian cattle (147) and coat colour may affect thermal exchange with the environment. Brobeck (148) suggests that temperature regulation is the function in terms of which body weight, food intake and activity are normally adjusted in interdependent fashion.

Consequential changes.—A variation with time, but no regular seasonal variation, was found in the blood composition of Louisiana dairy cows (149). A significant seasonal variation in the extracellular fluid volume occurs in monkeys as in man (150). Heat inhibition of diuresis in dogs was found to commence before polypnoea (151), and there is some evidence that this is mediated by the posterior pituitary hormone. That certain animals (antelope, gazelle (152), desert rat and koala) seldom drink, even in hot regions, continues to exercise the imagination, and calls for balance studies. The relative importance of night as opposed to day-time feeding in hot weather has been demonstrated for cows (153) and chickens (154). Anorexia may be a limiting factor in the continued exposure of dairy cows (155) and chickens (156) to temperatures not sufficiently great to produce hyperthermia. Rodbard (157) finds a direct relationship between body temperatures and arterial pressure from amphibia up.

In cold climates, longer days are associated with increased fertility and mating in most animals (158), but in temperate to hot climates fertility often declines in summer (159), except apparently in Zebu cattle (160). The well-known direct effect of temperature upon spermatogenesis has been regarded as the explanation for this, but Bogart & Mayer (161, 162) appear to have shown conclusively that, in rams at least, a seasonal hypothyroidism (presumably thermoregulatory) is the main factor. Administration of thyroxine as thyroid-active protein abolishes "summer sterility," while thiouracil will induce "summer sterility" in fall beasts. The conception rate of cattle may fall a few days after commencing dosage, but rises well above previous levels and continues thus for some days after cessation (163). Possible cooling of the avian testis by the abdominal air-sac is reported (164). Seasonal variation in egg production is described by Parker (165). Hypothermia leads to premature laying of soft-shelled eggs by hens (166) and may induce twinning (167). Heat also leads to marked thinning (168) of shells or even soft shells, conditions not prevented by increasing the available calcium of the diet (169, 170). While milk volume was reduced in association with anorexia by continuous exposure of cows to severe heat, fat percentage was unaltered; neither were affected by limited though repeated exposure (155). Thyroid feeding may be accompanied by increased milk (171) and egg (172) production if a sufficient increase in food is given (173).

Modifying factors and tolerances.—While the specific dynamic action affects basal heat production, it seems to have little or no effect upon the heat tolerance of either animals or birds. The caloric value of the diet, on the other hand, has a strong and important effect as evidenced by rises in rectal temperature, pulse rate, respiratory rate and evaporative loss (174, 175, 176). While noticeable at normal air temperatures, the effect of increased feeding increases with temperature. If the diet is reduced, the effects disappear more rapidly than could be explained by changes in body form. The parts played by digestive processes, tissue metabolism and subcutaneous fat in these reactions have not yet been determined. Ring (177) does not support earlier suggestions that dietary fat has less effect than carbohydrates.

Homeotherms fall into four groups (134) as judged by normal and maximum body temperatures: (*a*) monotremes: labile normal *ca.* 83°F., upper safe limit of 102°F.; (*b*) marsupials and edentates:

less labile normal 93 to 95°F., upper safe limit of 103 to 107°F., (*c*) other mammals: fairly stable at values varying with species from 97 to 102°F., upper safe limit of 107 to 110°F.; (*d*) birds: more labile normal 105 to 107°.F., upper safe limit of 113°F. Within a group there is considerable species difference with little obvious evolutionary plan, and no high correlation of normal with upper lethal body temperature. Morrison (178) contributes observations on the homeothermy of Central American mammals, using stress-strain diagrams; while the thermal behaviour of some of Australia's monotremes and marsupials is reported from the writer's laboratory (179). Interest continues in the important question of the relative resistance of different species of domestic animals to the direct and indirect effects of tropical climates. Rhoad's heat-tolerance test (180), in spite of its limitations, is still the most practical field measure. Reports (176, 181, 182) continue on the increased tolerance conferred upon European breeds of cattle by an infusion (one eighth to one half) or Zebu stock; on the relative tolerance of European breeds (138, 183, 184); and on Yak hybrids (185). Macgregor again draws attention to the limitations of the swamp buffalo as compared with the river (Indian) buffalo (186). Fat animals do less well than lean ones (126) in heat. A certain degree of heritability of heat tolerance in cattle is reported (187).

Sturkie (135) found chickens to die in 50 to 90 min. in water at 6° to 12°C., the lethal body temperature for hens being 22.8 to 23.6°. and cocks 19.4 to 22.2°C. Hens were able to tolerate water at 20 to 28°C., with a body temperature of 27.8 to 28.9°C., for thirty-five to forty-four hours.

Spealman's observations (188) indicate that the heat-regulatory powers of rodents towards cold are inferior to those of large dogs and other larger mammals such as man (122) in that, upon immersion in water, the body temperature falls below 30°C. in the former as against 20°C. in the latter. The lower limit of body temperature is also much less (15°C. for rodents, 27°C. for dogs). Other workers (189), however, report successful rewarming of dogs cooled to a rectal temperature of 14.8°C. The lability of rodents is apparent in other metabolic experiments (117) and their low lethal temperature has been previously reported (190, 191). It is possible that these features are related to evolutionary position rather than to body size. To characterize homeothermy, therefore, the limiting

values for body temperature must be expressed as well as its rate of change with environmental heat stress. Cowles (192) in revising his previous opinion, suggests that fur and feathers arose in evolution as an insulation against solar radiation and became associated only secondarily with cold resistance.

The effect of external water and shade upon animal reactions is reported (193, 194). In dogs, Galvão (195) indicates that the basal metabolic rate does not follow the surface-area law in the tropical zone, and Ederstrom (196) shows the effect of age upon thermoregulation. Species difference in the effect of temperature upon phagocytosis is reported (197).

Climatology

Methods.—Amongst the numerous basic techniques involved in climatological work, certain ones additional to those already mentioned are noteworthy in the study of infrared radiation (198); sweat glands (199); clothing, skin and tissue temperatures (83, 200 to 203); respiratory measurements (204, 205); evaporative water-loss (206); exercise performance (207, 208, 209); calorimetry (210, 211, 212) and ventilation (213, 214).

An excellent compilation issued as a service report by the USAAF Aero-Medical Laboratory (103) gives a full account of the theory and practice of calcualting solar radiation intensity at sea level and various altitudes. Certain other aspects are dealt with by Hutchinson & Chapman (215). A simple method of calculating heat-loss from a surface (216) and the relationship between life and thermodynamics (217) are discussed.

Thermolytic assessment.—Progress continues slowly along three lines in the attempt to provide a general answer to the question, "What is the thermal significance of a given environment for a given individual?" The effective temperature scheme, leader of the empirical assessments, although confined to man, is continually subject to criticism. There seems to be little doubt that at moderate temperatures, humidity has much less effect upon comfort than the charts would suggest (95), as might be expected, since the water available for evaporation is limited to a small relatively constant amount. By substituting the globe thermometer for the dry bulb temperature in the effective temperature, Bedford (218) finds that the effect of moderate diffuse radiation can be incorporated in the assessment in satisfactory agreement with the direct findings

of the ASHVE workers (219). (Where radiation comes from a source of limited projection, compensation can be effected by the use of two globe thermometers, one shielded from the source, and the application of approximate geometric methods.) The shielding of thermocouples from radiation is discussed by the ASHVE workers (220). Thermodynamic assessments (221) await first, a determination of the appropriate mathematical function to be used in relating the thermal acceptance of the atmosphere and the heat production by the body; second, a decision upon the standard of reference or the position of the zero point for the equation; third, upon better establishment of the constants involved. Both the Rochester (222) and the Fort Knox (223) workers have advanced mathematical approaches. In the meantime, systematic plotting of animal reactions, under a variety of conditions, to standard combinations of atmospheric variables permits the accumulation of data against which any proposed method of assessment must be checked.

Immediate practical demands for a simple assessment of the thermolytic value of the environment brings, on the one hand, a suggestion to use an average of dry and wet bulb temperatures as a rough measure of effective temperature (224); and on the other, a new instrument, the sol-air thermometer (225), to measure the cooling load likely to operate upon building structures. It would appear that the data given by this instrument would be applicable only to the particular location in which it was erected. Missenard (226) has published a small popular account of thermolytic assessment. For agricultural purposes Prescott (227) advocates modifying the usual linear matching of precipitation to evaporation.

Settlement.—The late war has done much to bring home the realities of tropical living, good and bad, to an important fraction of dwellers in more temperate climes. There is a growing realization that, once the special problems of infectious tropical disease are overcome, hot climates per se are not the absolute barriers to white settlement they are commonly represented to be. There are few special nutritional requirements (61), a high level of physical performance has obviously been possible, and the incidence of heat stroke and allied conditions is much less than in the course of heat waves in temperate climates (54, 55). On the other hand, a high incidence of "dermatoses" (46 to 49, 111) and a reduction of

mental initiative (111) are evident. One must agree, therefore, with the conservative writers to up the point that it is more difficult for a freely operating white population to maintain the full level of productive efficiency characteristic of temperate latitudes; but one must disagree firmly with those who would extend this as a severe and absolute limit to tropical settlement. If a sufficient reason for settlement exists, selection of personnel, community organization and active counteraction of isolation can largely discount the disadvantages, as they have in other initially undesirable localities (221). The writer must particularly disagree with statements (228) that "a hot and specially a moist climate tends to impair their (young children's) vigour so that they may be less robust than children at home." The effect of individual experience upon judgment of the "ideal" climate is shown by contrasting Brunt's 66 to 68°F. and 60 per cent relative humidity (229), with American air conditioning recommendations of environmental temperatures up to 78°F. (92, 93, 94). Air conditioning would undoubtedly be of advantage in the tropics (230), but not to the point of attempting to create a temperate climate indoors. Bedrooms (126), kitchens, and offices call for some relief. Bedford discusses the problem of the industrial worker in India (231).

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PHYSIOLOGY OF SWEATING

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In the past few years research on sweating has followed three different trends. Firstly, the recent war stimulated work on sweating in relation to thermoregulation and water balance. Problems of this type assumed practical significance for the activities of soldiers under various climatic conditions, such as in the jungle, desert, and in arctic surroundings. Secondly, the biochemistry of sweating aroused considerable interest, especially in regard to the excretion of chlorides and vitamins in the sweat. Finally, regional changes of sweating have proven to be indicative of disturbances of the vegetative innervation. As war experiences and recent developments in sympathetic surgery have demonstrated, circumscribed loss of sweating has great diagnostic importance in lesions of the peripheral and thoracolumbar nervous systems.

Sweating and Thermoregulation[1]

Body heat is dissipated by radiation, convection, and evaporation. Below 88°F. (31°C.) and under resting conditions, the evaporative heat loss is small and amounts to approximately 25 per cent of the metabolic heat [Newburgh and Johnston (2)], but at higher temperatures the evaporative heat loss increases rapidly.

Insensible loss of water through the skin.—It is probable that practically all evaporation below 88°F. is an insensible loss of water; it amounts to approximately 20 to 30 gm. per hour. According to Whitehouse, Hancock, & Haldane (3) insensible loss of water is due to osmosis since it is decreased by immersion in water, but increased by immersion in concentrated saline solution. Burch & Winsor (4, 5, 6) stated that the insensible loss of water occurs by diffusion through the keratinized layers of the skin. The rate of diffusion is about the same through the living or dead skin. These authors consider the term "insensible perspiration" a misnomer, because insensible water loss is not an active secretory process. Tennent (7) observed that in the rat most of the water

[1] An excellent and comprehensive review on this subject is presented by Ladell's (1) paper.

loss through the skin is due to diffusion, since these animals have only a few functional sweat glands.

Stimulus to thermal sweating.—Evaporative loss of water above 88°F. is accomplished by sweating, that is, by active secretion of the eccrine sweat glands. Sweating is brought on by the combination of elevated skin and rectal temperatures and, as a rule, starts in nude subjects when the skin temperature exceeds 94°F. In an unacclimatized individual the rectal temperature may rise considerably before sweating begins, but in an acclimatized person sweating starts as soon as the rectal temperature is only slightly raised [McArdle (8)]. According to Adolph (9), initiation of full sweating is delayed for five to fifteen minutes after hot air impinges on the skin. The skin warms up immediately, but that stimulus speeds up the rate of evaporative loss only two and a half times; in other words, the local heat stimulus yields only a moderate sweating response. If, however, the total heat accumulation of the body has reached a certain point and the rectal temperature increased approximately 0.2°C., profuse sweating occurs which may multiply the evaporative water loss tenfold. The rate of acceleration of sweating depends on the environmental temperature and the degree of humidity present. Randall (10, 11) confirmed Adolph's observations and found that the initial outbreak of sweating following thermal stimulation is due to an increased number of activated sweat glands; the profuse perspiration in the later stage is explained by a large increase of sweat output of individual glands. Randall also noted simultaneous peaks and depressions in the number of functioning sweat glands (on the forearms). This observation suggests the presence of a bilaterally and periodically discharging sudomotor center. Thermoregulatory sweating may be elicited in two different ways: first, the sudomotor centers may be directly stimulated by overheated blood reaching them; secondly, the sudomotor center may be also indirectly activated by means of reflexes from afferent cutaneous and visceral impulses. This is supported by the following observations: if one arm is exposed to radiant heat, it starts to sweat; later on, when the thermic stimulation becomes intense, sweating occurs on the other arm to a lesser degree (Randall). If the extremities are heated, but their circulation arrested by tourniquets, there is no sweating until the tourniquets are released, and thus the warm blood is able to reach the brain. On the other hand, if the legs of a paraplegic person are im-

mersed in hot water, sweating does not start until the rectal temperature is very much higher than it is at the onset of sweating in a normal individual [Carmichael (12)].

Rate of Sweating

Eichna and co-workers (13) recorded sweating as high as 3 l. per hour over short periods. McArdle found in resting individuals values of 8 l. in a four hour period at 100°F. dry bulb, and 94°F. wet bulb. Clothed subjects may sweat at this rate when the temperature is 10° lower. For short periods (thirty minutes), the sweat glands may secrete 60 to 70 cc. per minute. The water loss at this rate cannot be replaced by drinking. Such high rates of sweating are mostly found under experimental conditions. However, Ladell, Waterlow & Hudson (14) found that in the Arabian desert men in shorts with moderate activity sweated 500 cc. per hour in the shade. Dill *et al.* (15) observed daily sweat losses in the Arizona desert reaching 10 l. Moss (16) observed coal miners losing as much as 8½ l. during a five-hour shift. A high rate of sweating is not maintained for a long time. Robinson & Gerking (17), and Gerking & Robinson (18) found an average rate of sweating for the first two hours of a six-hour exposure 1.31 kg. per hour, for the last hour only 0.89 kg. per hour. This falling off in the sweating rate may be due to fatigue of the sweat glands. It is certainly not caused by dehydration, since it occurs even in conditions in which the loss of sweat is completely replaced by water. The maximal rate of sweating may not correspond to the highest rectal temperature; the rate with which the rectal temperature rises is more significant. Moderate water deficiency has no influence on the rate of sweating [Eichna *et al.* (13)], but sweating is arrested in severe dehydration. Drinking of water equal to the sweating loss [Johnson, Pitts & Consolazio (19, 20)], or in excess of it [Ladell (1)], does not influence the rate of sweating. Intake of saline solution decreases sweating when the salt intake exceeds the salt loss in the sweat; for example, Ladell (1) found that clothed men sweated equally in four hours, whether they were drinking 0.1 per cent or 0.2 per cent sodium chloride solution, but they sweated 14 per cent less when drinking a 0.5 per cent saline solution. Sweating may be markedly reduced under pathologic conditions, such as in heat stroke, and in anhydrotic heat exhaustion. Wolkin, Goodman & Kelley (21) observed eight soldiers in the African desert showing

a complete failure of sweat mechanism. After a period of excessive perspiration, sweating entirely ceased below the neck, whereas the head and neck continued to sweat profusely. The anhydrotic skin had a goose-fleshlike appearance and sometimes exhibited brawny papulous eruptions with later desquamation. Body temperature and blood chloride level remained normal in these cases. The condition became aggravated by sunlight, but could be cured by keeping the patient in cool surroundings. The authors assumed that overexertion of the thermoregulatory mechanism is responsible for a reversible exhaustion of sweat glands. Similar cases were described by Novy & Ramsay (22), and Allen & O'Brien (23) in the South Pacific. Histologic studies by the latter authors showed the ducts of the sweat glands obstructed by hyperkeratosis, leading to an actual rupture of the ducts, pressure atrophy of the gland cells, and absorption of the sweat by the lymphatics.

Regional distribution of sweating.—Even though thermoregulatory sweating is generalized, its distribution is uneven over various regions of the body. Kuno (24) found a high rate of sweating over the forehead, neck, trunk and dorsal surfaces of the hands, whereas the palms of the hands and soles of the feet showed the smallest sweating rate. Sodeman & Burch (25) measured the water loss from various parts of the body and charted the findings as a profile graph in conditions of rest in comfortable or hot wet climates, both in normal and diseased persons. Maximal thermogenic sweating was encountered at the fingers, arms, axillae and forehead. Weiner (26) measured the sweating over thirty small skin areas, confirming Kuno's findings. He found maximal sweating on the trunk, less sweating on the head, and, in decreasing scale, arms, feet and hands. The sweat rate diminishes distally at the extremities, with the exception of the dorsum of the hand, which shows a higher sweat rate. Approximately 50 per cent of the sweating comes from the trunk, 25 per cent from the legs, and the remaining 25 per cent from the head and upper extremities. The local differences in sweating rate depend on variations in the number of sweat glands and on the variable activity of individual glands. Randall (10, 11) studied the activity of sweat glands in a given skin area by a colorimetric method (iodine starch reaction). He found that maximal stimulation of all sweat glands could be obtained by iontophoresis of mecholyl (acetylbetamethylcholine hydrochloride). Thermal stimuli proved to be less effective, unless they were pro-

longed and very intense. Between an environmental temperature of 20 to 35°C., the sweat glands on the extensor surface of the forearm secrete phasically with alternating periods in which large and small numbers of glands are successively functioning. The periodicity and the number of glands participating in each cycle vary depending on the outside temperature, visceral and peripheral stimulation, and also on the emotional state of the individual. With a resting person at comfortable temperature, sweating consists of a sudden activation of a number of sweat glands for a few seconds, followed by a period of little or no sweating. The secretory phase of the individual gland is short; in a given area activity may alternate between many glands, thus prolonging a given sweating cycle. Intensive heating increases both the number of secreting glands and the amount of output of the individual glands.

Influence of climate, clothing and acclimatization.—Ladell (1) found that in hot wet climate without much wind only a small portion of the sweat is evaporated. For instance, fully equipped soldiers working at 95°F. dry bulb, and 85°F. wet bulb, evaporated less than 30 per cent of their sweat when air movement was slight. Clothing absorbed 50 per cent of its weight in sweat, but when air movement increased to ten miles per hour the effect of evaporation increased 45 per cent. When sweating fatigue diminishes the loss of water, the individual still perspires sufficiently for adequate evaporative cooling. Burch (27) noted that in hot wet climates persons with congestive heart failure sweat 27 to 47 per cent less than normal individuals. The sweating rate returns to normal when the cardiac decompensation is overcome. Belding and others (28) studied the thermal responses and efficiency of sweating when men dressed in arctic clothing were exposed to extreme cold. Most of the evaporated sweat is absorbed in the clothing. The authors assumed that the transfer of sweat from the skin depends on differences in vapor pressure from layer to layer, and on specific resistance to vapor transfer provided by the fabrics and air trapped in the clothing. Because the vapor pressure difference between the relatively warm inner layers of clothing and the cool outer layers is large, little moisture is picked up unless sweating is profuse. The vapor pressure difference between the cool outer layer and the surrounding air is small, resulting in an accumulation of sweat in the outer garments. Sweating is an inefficient way of body cooling when men are heavily dressed in the cold because the originally

evaporated sweat is recondensed in the clothing, returning the heat of condensation to the skin. During walking at 0°F. sweating efficiency is greatest (60 to 75 per cent) at low sweating rates, and least (40 per cent) at a profuse sweating rate. When the activities in arctic climate are reduced to the point that men feel cool but comfortable, sweat production and its accumulation in the clothing are reduced to a minimum. McArdle (8) observed that with successive exposures to heat sweating starts at a lower temperature than before; eventually the rate of sweating at a given rectal temperature increases.

Chemistry of Sweating

Chloride concentration in the sweat.—The mineral content of sweat shows considerable variations. Dill and co-workers (15) found 0.088 gram chlorides per 100 cc. Johnson, Pitts & Consolazio (19, 20) stated that the sweat is isotonic with the plasma. Ladell, Waterlow & Hudson (14) found variations in chlorides from 0.1 gm. to 0.6 gm. per cent with an average figure of 0.29 per cent. Lobitz & Osterberg (29) observed even higher chloride values in the palmar sweat; namely, 0.65 to 1.45 gm. per cent. These considerable differences may be partially due to the techniques employed. The following methods have been used for chemical determination: first, all sweat is collected by washing the body surface and the chloride measured; secondly, a twenty-four-hour chloride balance is made and the chlorides in the sweat calculated by subtracting the chloride loss in urine, feces, and vomitus; thirdly, the most commonly used method measures the chlorides in the sweat collected from one extremity enclosed in an impermeable envelope. The average chloride rate is then determined by calculation. This method is unreliable since the sodium chloride concentration of the sweat varies over different parts of the body. Mickelsen & Keys (30) found differences up to 100 per cent between the sweating of the arm and that of the trunk. Ladell (1), however, stated that the total loss of sodium chloride can be fairly well estimated by using a sufficiently large area of body surface for sampling. During a single exposure to heat, the chloride concentration of the sweat rises steadily and is independent of the level of rectal temperature [Ladell (1), Johnson, Pitts & Consolazio (20)], but the chloride loss increases proportionally to the elevation

of skin temperature. The greater the rate of sweating, the higher becomes the concentration of chlorides. The chloride concentration in the sweat is decreased by salt deficiency and increased by high salt intake [Ladell, Waterlow & Hudson (14)]. There seems to be no parallelism in the chloride level of blood and sweat. The effect of acclimatization on the chloride concentration in the sweat is controversial. Dill (15) and Mickelsen & Keys (30) found diminution of chlorides in acclimatized individuals. Ladell (1) observed at first an increase, later a drop of chlorides, presumably due to a lowered salt intake. Johnson, Pitts & Consolazio (20) attributed the drop in chloride values to a decrease of rectal and skin temperatures. With increased acclimatization the sweat glands are less apt to fatigue. Desoxycorticosterone reduces the chloride loss considerably (25 per cent according to Ladell). Moreira, Johnson & Forbes (31) stated that adrenal cortical extract has a similar effect.

The level of nonprotein-nitrogen in the sweat [Talbert, Silvers & Johnson (32)] and the lactate level [Mickelsen & Keys (30)] may be much higher than that in the blood. The pH of sweat shows considerable variations; sweat is alkaline when secreted but becomes acid in contact with the skin. Weiner (26) found diminishing acidity as the secretion continues.

Excretion of vitamins in the sweat.—As to the excretion of vitamins through the skin, observations of different authors have been rather contradictory, probably due to differences in techniques employed. Johnson, Hamilton, Mitchell, Spector, and others (33 to 39) investigated the secretion of the following substances in the sweat folic acid, nicotinic acid, nicotinamide, nicotinuric acid, pyridoxine, pseudopyridoxine, 4-pyridoxic acid, pantothenic acid, ascorbic and deshydroascorbic acid, potassium iodide, inositol and para-aminobenzoic acid. They found a significant loss of pantothenic acid in the sweat, and possibly also, of deshydroascorbic acid. On the other hand, Kirch, Cornbleet & Bergeim (40) found only traces of ascorbic acid and deshydroascorbic acid in such small amounts that vitamin C deficiency is not likely to result from heavy sweating. Mickelsen & Keys (30) observed considerable loss of nicotinic acid in sweat. Sargent, Robinson & Johnson (41) concluded that there is no significant loss of water soluble vitamins in the sweat and that under severe tropical conditions the vitamin excretion through the urine by far exceeds that through perspiration.

Neurophysiology of Sweating

Since sweat secretion is controlled by the vegetative nervous system, observations of sweating responses in normal individuals and those with known neurologic lesions have contributed much to our anatomic and physiologic knowledge of the vegetative pathways.

Methods.—A number of qualitative and quantitative methods are suitable both for physiologic and clinical purposes. Colorimetric methods, such as Minor's iodine starch test, or Guttmann's quinizarin test, have been clinically well established by virtue of their simplicity and striking color contrast [Rose (42)]. Silverman & Powell (43, 44) made sweating visible by an ink reaction occurring in a mixture of iron salts and tannic acid when moisture is present. The skin surface to be tested is painted with an alcoholic ferrichloride solution, then dried, and finally dusted with tannic acid powder. The ink reaction occurs when sweating is induced. A modification of this method is particularly suitable for the study of palmar sweating: after the skin of the palm has been prepared with the iron salt solution and dried, the hand is placed on paper impregnated with tannic acid, thus producing an ink fingerprint. Still simpler for the demonstration of palmar sweating is Walker & Netsky's (45) prism method: the skin to be investigated is pressed against one plane of a prism with total internal reflection. If light is then thrown through the second face of the prism, a sweat print may be observed and photographed through the third face of the prism.

Another widely used method is based on the observation that galvanic skin resistance depends largely on sweat secretion [Richter (46) and Jasper & Robb (47)]. Since anhydrotic areas possess an extremely high skin resistance, they can be mapped out from the surrounding sweating skin. This situation obtains in complete lesions of the peripheral and thoracolumbar sympathetic nervous systems. The accuracy of the skin resistance method is enhanced by diaphoretic procedures. On the other hand, it should be kept in mind that the skin resistance method is not a specific indicator of sweat secretion since the galvanic resistance also varies with a changing state of vascularization. For neurologic study, most authors induce sweating by heat, since thermoregulatory sweating depends on the activation of central sweating pathways. Some investigators have employed parasympathomimetic drugs as

diaphoretic agents.[2] Guttmann (48) recommended the use of furmethide which, in intramuscular doses of 3 to 5 mg., produces generalized sweating with fewer side effects than pilocarpine or mecholyl. The drug is chemically not related to acetylcholine, but its action can be inhibited by atropine.

Sweating in peripheral nerve lesions.—Recent war experiences afforded an ample opportunity of studying sweating in peripheral nerve injuries. In total nerve interruption the area of anhydrosis is almost identical to that of sensory loss. Some diagnostic difficulties may arise in incomplete nerve lesions and in cases with signs of regeneration or with anomalous innervation.[3] Under such conditions Highet (49) obtained diagnostic information by procaine blocks of the intact neighboring nerves, or of the affected nerve. He thus determined the autonomous and maximal sweating zones of the affected nerve and overlapping innervation from neighboring nerves. Arnold (50) studied sweating responses in patients with leprous skin lesions following intradermal mecholyl injection; sweating was usually decreased in the anesthetic areas. Neumann and co-workers (51) investigated in cats the return of sweating following crushing or section with resuture of peripheral nerves. After section and resuture of a nerve, sweating began to return after fifteen to thirty weeks, and increased gradually to reach 40 per cent of the normal output after forty-one weeks. Following nerve crushing, sweating returned after fifteen weeks and increased to 69 per cent of normal after nineteen weeks. In other words, the return of sweating function was twice as rapid after crushing than after nerve section and resuture. Jasper (47) observed extreme elevation of skin resistance three weeks following

[2] Hexadienol applied to the skin produces local sweating. Since it causes no generalized parasympathetic stimulation and is free of toxic side effects it has been recommended for diagnostic purposes in the form of a special iodized hexadienol starch mixture. The agent has a muscarine-like effect on peripheral cholinergic receptors and its action can be inhibited or abolished by atropine (Koppani, T., *J. Am. Pharm. Assoc.*, **34**, 221–24, 1945).

[3] Another example of anomalous innervation may be the "auriculotemporal syndrome," consisting of hyperhidrosis, vasodilatation and pain in the distribution of the auriculotemporal nerve and parotid region during gustatory stimulation. Two such cases have deen described following injury of the parotid region. The mechanism of the response is assumed to depend upon local sensitization or hyperirritability of cholinergic effectors and diffusion of acetylcholine from neighboring salivary glands during gustatory activation (Langenskiöld, A., *Acta Chir. Scand.*, **93**, 294–306, 1946).

peripheral nerve section. Later on the skin resistance fell gradually to a steady level, which was still higher than that of the normal skin.

Sweating in lesions of the sympathetic nervous system.—Analysis of sweating disturbances following various types of sympathectomy has given valuable information on the anatomy and physiology of the thoracolumbar system. Ray, Hinsey & Geohegan (52) investigated the sympathetic innervation of the upper extremity by means of the skin resistance method, following stimulation and section of anterior spinal nerve roots. According to these authors, in man the sympathetic supply for the hand passes through the first to the tenth thoracic nerve roots. As many as seven spinal segments may contribute to the innervation of sweat glands of one finger. It is assumed that within the sympathetic chain ganglia many preganglionic fibers converge onto a single postganglionic neuron. Even after complete section of all anterior roots containing preganglionic fibers, slight sympathetic activity returned after the tenth week. This is probably not caused by regeneration, but presumably due to rearrangement or supplementation via roots which previously showed no sympathetic activity. Walker & Netsky (45) studied sweating responses by the prism and colorimetric methods after the Smithwick type of upper dorsal sympathectomy. They confirmed the observation of Ray and co-workers and stated specifically that the first thoracic root carries sweat fibers for the upper extremity. Sweating in areas denervated by preganglionic sympathectomy could be elicited at any time by pilocarpine for at least two years postoperatively. Richter (53) analyzed a series of forty-five dorsal sympathectomies and six stellate ganglionectomies by the skin resistance method. There was wide variation in the size of the denervated skin areas. Their borderlines correspond roughly to those of the sensory dermatomes. Most upper thoracic ganglionectomies denervated the hands, but failed to denervate the central portion of the face. In stellate ganglionectomy, denervation of the upper extremity was usually incomplete, but that of the face nearly complete. Sympathetic denervation of the hand depends largely on the removal of the second dorsal ganglion. A few days following sympathectomy, sympathetic activity may be temporarily increased in the denervated areas. In forty-eight thoracolumbar sympathectomies (removal of D9 to L1), Richter & Otenasek (54) found irregular bandlike areas of anhydrosis in the

lower abdominal region. Differences in size and shape of these areas were explained by irregular and asymmetrical distribution of the posterior and anterior primary rami of the intercostal nerves and their widespread overlap. In more complete dorsolumbar sympathectomies (55) (technique of Poppen with removal of D4 to L3 or L4), there was anhydrosis of the lower trunk and of the lower extremities, but some sweating was preserved in the groin and upper thigh. The fact that these areas could be made anhydrotic by additional section of the anterior twelfth thoracic and upper three lumbar roots suggests that some of the sweat fibers for the thigh and groin travel directly via anterior nerve roots to the periphery, without passing through the dorsolumbar chain [Ray (56)].

The effect of stimulation of the sympathetic chain on sweat glands of the rat was studied by Richter & Whelan (57). Single induced shocks applied to the lumbar chain caused a galvanic current to be given off by the hind foot pads. This response was monophasic, with a latency of 0.6 seconds, and a duration of 5 seconds. The threshold was greater for the make than for the break. Induced shocks at a rate of 136 to 375 per minute (2 to 6 per second) sufficed to obtain complete tetanization of sweat glands.

Sweating in lesions of the spinal cord.—List & Pimenta (58) investigated in man spinal reflex sweating, a pathologic type of sweating associated with severe or total transverse lesions of the spinal cord. The authors interpreted this type of sweating as a release phenomenon and a component of the spinal mass reflex. It is induced by any afferent stimulus acting on the portion of the cord distal to the lesion. Its efferent mechanism is also mediated by the distal stump of the cord, and peripherally by the thoracolumbar system. If the site of a transverse lesion is known, the lower level of thermoregulatory sweating and the upper level of spinal sweating may be used to study the spinal segmental (preganglionic) innervation of sweat glands. The dermatomes for sweating are much larger than the corresponding sensory dermatomes. As to the anatomic localization of thermoregulatory pathways in the spinal cord, Beaton & Leininger (59) found that in *Macaca mulatta* the sudomotor fibers pass through the lateral and anterolateral columns. The pathways are predominantly crossed with the decussation of fibers in the cord occurring close to the

level of the preganglionic outflow. These findings differ from clinical observations, which indicate a predominantly ipsilateral course of the descending spinal sweat fibers [List & Peet (60)].

Emotional sweating.—Clinicians have been impressed by the fact that palmar and plantar sweating is associated with the emotional state of the individual rather than with thermoregulation. Silverman & Powell (61) recorded palmar sweating in eleven hundred soldiers with the ink print method, and noted excessive degrees of palmar sweating with emotional disturbances, such as anxiety or tension states. Palmar sweating is centrally controlled by the cortex or the hypothalamus. It occurs whenever activity is anticipated, and its physiologic purpose may be to prepare the hand for the act of grasping. Richter, Woodruff & Eaton (62) observed that the palms and soles normally show sharply defined areas of low galvanic resistance. During sleep and exposure to cold these areas contract, but they expand during the waking state, excitement, and on exposure to heat. The "hand-foot patterns" presumably are representative of cortical or subcortical rather than of peripheral innervation.

Sweating in cerebral lesions.—Relatively little is known about modification of sweating in cerebral lesions. Bucy & Pribram (63) described a case of right sided posterior frontal oligodendroglioma in a patient who had left facial Jacksonian attacks accompanied by sweating of the left side of the face and left arm. This and similar observations of the literature suggest that the precentral cortex exercises some focal control on sweating.

Fisher & Stravaky (64) stated that injection of mecholyl in patients with cerebral lesions (especially in the frontal and premotor areas) may produce signs of sympathetic irritation on the contralateral side, consisting of widening of the pupil, blanching, coldness and diminished sweating. It is assumed that these phenomena are due to sensitization of the partially isolated supraspinal sympathetic centers.

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PHARMACOLOGY

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Many of the significant researches of pharmacological interest carried out during World War II have been reviewed in the past few years. Cooperative investigations conducted under the auspices of the Office of Scientific Research and Development and the various Armed Services during the recent war have resulted in many notable advances in the field of pharmacology. Much of the work was in the nature of finding an answer to urgent problems. For that reason, considerably more in the way of financial support was given; consequently, larger numbers of animals could be used resulting in more complete and more accurate data than are often obtained in such studies. Certain new groups of compounds were also brought to light and new chapters are being opened in pharmacology. Many of the compounds were primarily studied during the war with a view to being useful in chemical warfare. In the course of events, possible therapeutic applications were discovered, as in the case of the nitrogen mustards.

The need for human volunteers was clearly shown in the investigations on antimalarial drugs, chemotherapy of syphilis, antivesicants, insecticides, and rodenticides. The results of these studies emphasized the necessity for careful clinical appraisal of new therapeutic agents and the field of experimental therapeutics has thereby assumed a role of major importance. Recognizing the need of pharmacological laboratories, whether academic or commercial, for assistance in securing competent clinical trials of new remedies, the Council on Pharmacy and Chemistry of the American Medical Association has established the Therapeutic Trials Committee. This committee is endeavoring to preserve and expand the benefits to pharmacology that accrued from wartime cooperative research.

A great deal of interest in the manner in which drugs produce their pharmacological action has arisen during the past few years. This new phase of pharmacological research has followed the rapid progress in the elucidation of the biochemical reactions which provide the energy for cellular function, and studies on the action of

drugs on enzyme systems may provide explanations for many of the responses obtained.

Pharmacologists, as well as other scientists, are making use of radioactive elements as tracers. Undoubtedly, many important observations will come to light in the near future especially with regard to compounds which cannot be identified by ordinary chemical methods.

With the many new techniques and precise instruments which are available for pharmacological research the emphasis has turned from the qualitative aspects to quantitative measurements which should be reflected in the development of more effective therapeutic agents and a better understanding of their uses and limitations in medicine.

Rodenticides

The search for new rodenticidal substances which was necessitated by an increased demand for such substances during the war led to the introduction of two effective rodenticides, alpha-naphthylthiourea (ANTU) and sodium fluoroacetate (1080). The toxicity of these and other agents employed for rodent control has been reviewed by Pfeiffer & Loew (1).

The efficacy of ANTU as a field poison for the control of Norway rats was observed by Richter and associates (2, 3) as a result of a systematic investigation of the toxicity of a number of thiourea derivatives. This investigation was stimulated by the observation of Richter & Clisby (4) that phenylthiourea was highly toxic to rats. Measurements of the toxicity of a large number of thiourea derivatives (3) led to several interesting findings regarding the relationship between chemical structure and toxicity among members of this series of compounds. Thus, introduction of a single aromatic radical attached to one of the thiourea nitrogens enhanced the acute toxicity of thiourea while two or more substituents, either on the same or both nitrogen atoms, lowered the toxicity as did substitution on the sulfur atom. It is interesting that the study of thiourea derivatives as antithyroid agents by Astwood and associates (5, 6) and by McGinty and co-workers (7, 8, 9) has centered around finding compounds with high antithyroid activity and low toxicity and the same changes in the thiourea molecule which make it less effective as a rodenticide enhance its value as an antithyroid agent.

Considerable effort has been directed toward ascertaining the biochemical changes which result from acute ANTU poisoning in animals in order to gain an understanding of the cellular reactions which are disrupted leading to pulmonary edema and pleural effusion which appear to be the immediate cause of death after acute poisoning by thiourea compounds. Studies on the carbohydrate metabolism of ANTU-poisoned animals by DuBois and associates (10, 11, 12) have shown that lethal doses of ANTU as well as other monosubstituted derivatives of thiourea resulted in marked hyperglycemia and depletion of liver glycogen. These changes appeared to be induced by epinephrine since they could be prevented by adrenal demedullation. However, prevention of the disturbance in carbohydrate metabolism had no effect on the development of pulmonary edema nor on the survival time of ANTU-poisoned rats. DuBois & Erway (13) found that ANTU is an effective inhibitor of tyrosinase and the copper-catalyzed oxidation of ascorbic acid *in vitro*. Although no role has been assigned to tyrosinase in mammalian tissues it seems significant that there was a correlation between the inhibitory action of several thiourea derivatives on this enzyme and their toxicity to rats. This finding suggests that the acute toxicity of ANTU may result from interference with some oxidative reaction in animal tissues.

Although no effective antidote for ANTU has yet been found Byerrum (14) noted that rats fed a diet high in iodine were able to withstand several times the LD_{50} dose of ANTU. However, iodine was ineffective in affording protection against ANTU when given simultaneously or after ANTU. Further studies by Byerrum & DuBois (15) have shown that the thyroid gland is involved in the protective action of iodide since no protection against ANTU was observed in iodine-fed thyroidectomized rats. This, however, did not appear to be due to conversion of iodide to di-iodotyrosine or thyroxin since neither of these compounds afforded more protection than an equivalent amount of inorganic iodide.

Sodium fluoroacetate has been the subject of numerous studies since its recent introduction as a rodenticide (16). These investigations have revealed considerable species variability in the site of action and susceptibility to the poison. The fluoroacetate ion does not exhibit the actions of other monohalogenated acetates (17, 18), being much more toxic and exerting specific actions on the myocardium and the nervous system. The toxicity and the species re-

sponse to fluoroacetate have been reported by Chenowith & Gilman (19).

Although fluoroacetate finds use as an effective rodenticide the high toxicity to all species studied presents the constant danger of accidental poisoning. The lack of an effective antidote for fluoroacetate poisoning intensifies the dangers accompanying indiscriminate use of this poison.

Insecticides

Foremost among new contributions to the field of insecticides has been the introduction of 2,2 bis(parachlorphenyl)-1,1,1 trichlorethane (DDT) into this country. Although DDT was synthesized in 1874 by Zeidler (20), its insecticidal action was only recently observed by Müller (21) and the widespread use of this substance for a variety of insects now indicates its superior value as an insecticide. Numerous investigations have been carried out on DDT in both animals and insects and it is only possible to mention a few of these studies in this review.

DDT poisoning in both mammals and insects manifests itself by symptoms which are primarily of neurological origin. In mammals a sufficiently high dose results in generalized tonic and clonic convulsions which may terminate with death (22, 23, 24). In addition to its neurological effects DDT produces hyaline degeneration and focal necrosis of the liver (23, 25).

The acute LD_{50} of emulsified DDT injected intravenously is between 40 and 75 mg. per kg. for the rat, rabbit, cat, dog, and monkey according to Philips & Gilman (24). DDT powder applied to the skin, however, is nontoxic to mammals unless it is applied in certain organic solvents (26). The average LD_{50} of DDT applied to the surface of the cockroach, fly, and mosquito is about 12 mg. per kg. (27, 28). Since the LD_{50} of DDT for the fly, cockroach, and mosquito, and for several mammals differs by a factor of only three to five times when the absorbed material is considered (28), it is absorbability which accounts for the large apparent difference in the toxicity of DDT to insects and mammals. The efficient absorption of DDT from the insect body surface as compared with the poor absorption through mammalian skin is an important factor in the excellence of DDT as an insecticide.

The wide usage of DDT presents the danger of contamination

of foodstuffs and consequent ingestion by animals. A treatment for acute poisoning and methods for measuring the DDT concentration of tissues was therefore desirable. Phenobarbital has been found (24) to be an effective antidote for acute DDT poisoning in mammals. Several assay procedures for DDT have been proposed. Laug (29) has devised a biological method depending upon the toxic response of the house fly by which quantities of DDT of the order of 2.5 p.p.m. can be measured. Chemical methods have also been devised among which is the colorimetric method of Schecter & Haller (30). Distribution studies on DDT in animal tissues have shown (31, 32) that fat contains a higher quantity than any of the other tissues and that a large percentage of ingested DDT appears in the feces.

Many studies on the mechanism of action of DDT have thus far failed to elucidate the exact biochemical site of action of the insecticide and it remains for future research to explain which metabolic reactions are disrupted by DDT. Derivatives of DDT are being prepared and studied with the hope of finding less toxic and more efficient ones.

Another insecticide whose use has been recently introduced into this country is hexaethyl tetraphosphate (HTP). This compound was first used by the Germans for the control of aphids as a substitute for nicotine. Since aphids are resistant toward DDT the use of HTP against these insects has proved efficacious in this country. DuBois & Mangun (33) first observed that mammals and insects poisoned by HTP exhibited symptoms characteristic of those produced by anticholinesterase drugs. Following this observation these investigators demonstrated that HTP exerts a strong inhibitory action on mammalian and insect cholinesterase. They also investigated a number of other organic phosphate esters and found that tetraethyl pyrophosphate (TEPP) was more toxic and possessed a stronger inhibitory action on cholinesterase than did HTP (33).

The toxicity of HTP and TEPP for mice, rats, and rabbits by different routes of administration has been determined (34, 35, 36). Rats are most sensitive to the oral administration of HTP, the LD_{50} by this route being 7.0 mg. per kg. (35). The LD_{50} for TEPP orally in the rat was found to be 2.0 mg. per kg. (36). Deichmann & Witherup (36) showed that HTP was readily absorbed through

the intact skin of the rabbit. Hagan & Woodard (35) observed that physostigmine gave rabbits some protection against the lethal actions of HTP.

Pharmacologic tests on HTP and TEPP have revealed (37) these agents to be essentially similar to physostigmine, neostigmine and DFP in their actions on structures innervated by the autonomic nervous system. Responses of the isolated rabbit heart and gut and of the cat's blood pressure to acetylcholine are markedly augmented. Symptoms of poisoning in animals are typical manifestations of parasympathetic over-stimulation. Atropine abolishes these effects and offers some protection against the lethal action. With these investigations a new group of cholinergic drugs have been introduced which seem worthy of further study.

Autonomic Drugs

The search for sympatholytic and adrenolytic drugs has resulted in the discovery of a number of compounds which give promise of therapeutic usefulness. Foremost among these are N, n-dibenzyl-β-chlorethylamine (Dibenamine) (38, 39), and 2-benzyl 4,5-imidazoline (Priscol) (40, 41, 42).

The pharmacological properties of Dibenamine have been studied in some detail by Nickerson & Goodman (43) who demonstrated that this agent blocks the excitatory responses of smooth muscle to sympathetic nerve stimulation and to epinephrine. They emphasized its specific, potent, and prolonged sympatholytic and adrenolytic actions. Doses which are highly effective in animals appear to lack important toxic actions, and the adrenergic blocking action persists for three to four days. It was found (43, 44) that Dibenamine protected rats and mice against highly lethal doses of epinephrine. However the drug did not prevent an increase in heart rate and cardiac output in response to epinephrine in the cat and dog (43, 45). Raab & Humphreys (44) showed that Dibenamine apparently does not interfere with the penetration and accumulation of injected epinephrine in the heart muscle.

Nickerson (46) has presented evidence that Dibenamine probably acts directly on the contractile mechanism of smooth muscle cells and not on their permeability.

Preliminary observations on human beings indicate that the actions of Dibenamine in man are closely parallel to those in animals. Clinical trials in diseases in which it is desirable to diminish

the peripheral vascular tone have given encouraging results (43). Tests made on hypertensive Goldblatt dogs, however, showed no definite beneficial effect of this agent on the blood pressure (47). Of clinical significance is the observation of Roemhild *et al.* (48) that in dogs Dibenamine improved the resistance to the development of irreversible hemorrhagic shock. They attributed this effect to the prevention by the drug of the usual prolonged vasoconstriction of shock. A group of related β-chlorethylamines, having an action similar to that of Dibenamine, has been studied by Loew & Micetich (49, 50).

Priscol has been examined pharmacologically by Ahlquist, Huggins & Woodbury (51) who pointed out its complex pharmacodynamic relationships. From their work and from that of others (40, 41, 42, 52) it appears that in some of its actions Priscol resembles the sympathomimetic agents, in others it resembles acetylcholine, in others histamine, and in still others the sympatholytic agents. It is of interest to note that in chemical structure this drug is closely related to both histamine and epinephrine. Furthermore, minor changes in the Priscol molecule produced the potent sympathomimetic agent Privine, which has also been shown to possess adrenolytic properties (53, 54). In its adrenergic blocking capacity Priscol is much less specific, less potent, and less prolonged in its action, than Dibenamine. A further disadvantage is that it has more side actions. In contrast to Dibenamine, Priscol has a marked vasodepressor action, which is thought (51) to be a sympathomimetic manifestation comparable to the depressor component in the action of epinephrine. In human subjects Priscol has been shown to increase the peripheral skin temperature in doses smaller than those required for sympatholysis or adrenolysis (55). It was suggested that this action of Priscol is histamine-like and is independent of its adrenergic blocking properties.

Extensive clinical investigations of Priscol are reported in the European literature beginning in 1939. Good results have been claimed in the treatment of peripheral circulatory disorders such as intermittent claudication, diabetic and arteriosclerotic gangrene, angioneurosis, acrocyanosis, Raynaud's disease, frostbite, Buerger's disease (56 to 59), nephritis (60), and as a diagnostic test for gastric function (61, 62). Schnetz & Fluch (63), in a critical evaluation, conclude that Priscol in a test drink is equal or superior to subcutaneous histamine in stimulating the production of the gas-

tric secretions. Reports of clinical results from the use of Priscol in circulatory disorders have not yet appeared in the American literature.

Considerable difference has been noted in the capacity of each of these agents to influence the responses to sympathetic vasopressor drugs in various species of animals. For example, in the cat and dog, Dibenamine regularly "reverses" the blood pressure response to epinephrine, while in the rabbit it has been reported that Dibenamine only abolishes the pressor effect (43). Observations on the chicken indicate that here Dibenamine has no influence whatever on the pressor response to epinephrine (64).

Since workers in this field have occasionally reported discordant results it seems possible that different experimental conditions, as well as the species of the animal, can explain some of the discrepancies.

Aside from their possible clinical application the newer adrenolytic agents constitute an improved pharmacologic tool for the study and differentiation of sympathicotropic drug action.

Antimalarials

At the outset of World War II, the accepted antimalarial drugs were quinine, quinacrine, and pamaquine. Quinine and quinacrine had been widely known and highly effective as suppressive drugs used to curb the acute attack. During the War it was proved that the prolonged use of quinacrine completely cures falciparum malaria. Pamaquine was too toxic for use by the military services.

The wartime research program for the development of synthetic antimalarial drugs was very extensive. This was necessitated by a loss of the source of 90 per cent of the world's supply of quinine to the Japanese shortly after the outbreak of the war. High quality medical care, extensive troop training, the use of insecticides, and the use of antimalarial drugs were responsible for maintaining a low death rate. A description of the organization of the research groups and their accomplishments has been published under the editorship of Wiselogle (65). A review of the principal wartime developments was recently published by Blanchard (66).

Among the new compounds studied during the War, chloroquine (a 4-aminoquinoline) was found to be superior to both quinine and quinacrine as a suppressive in that it will cause the disappearance of parasites more quickly and consequently clear

up clinical symptoms sooner. At the recommended dosage, relatively few toxic symptoms are encountered. Furthermore, it produced no discoloration of the skin.

Another suppressive drug superior to atabrine and quinine is paludrine, a biguanide compound. It has the advantage of a wider margin between the effective therapeutic and the toxic dose than has chloroquine, but the disadvantage of requiring a longer period of time to curb an attack in some cases. Hawking has shown that paludrine per se is inactive; it is converted in the body to an unknown metabolite which is the active antimalarial agent (67).

A third drug, pentaquine, an 8-aminoquinoline related to pamaquine, was found to be curative when administered simultaneously with quinine against South Pacific vivax malaria. These three new drugs represent the most effective compounds for malaria therapy and were selected from over 17,000 studied intensively during the past five years.

Antifilarials

A wartime need for effective antifilarial compounds led to the organization of a coordinated research program under the auspices of the National Research Council. Results of animal experiments have recently been reported (68 to 71). To date, the most effective compounds studied are a number of cyanine dyes. These compounds kill the adult worm both *in vivo* and *in vitro*, probably by inhibiting one or more of the enzymes concerned with oxidative metabolism.

The Nitrogen Mustards

During the recent War while man's attention was focused on finding new and more efficient ways to exterminate his fellow man, a poison was studied which now promises to be a life-saving tool in the treatment of cancer. These potentialities were indicated in studies (72) which showed that this group of toxic chemicals known as the nitrogen mustards particularly attacked the hematopoietic tissues of the animal while seemingly sparing others. It was later shown (73) that the gastrointestinal tract was also injured. Further studies which are summarized by Gilman & Philips (74) disclosed that all rapidly proliferating normal tissues are attacked by these substances and that these substances belong to the now rapidly growing group of compounds known as "mitotic ar-

restors" (75, 76). Clinical trials (77 to 80) with these substances have shown that while no cure of cancer is possible with these substances remissions of rather long duration may often be obtained in cases of Hodgkin's disease and lymphosarcoma. In several cases of such diseases where x-ray therapy was no longer of benefit, the nitrogen mustards were found temporarily beneficial and capable of making the tumor again x-ray sensitive. The hope that the continued use and study of the cellular effects of these substances will lead to a better understanding of cancer and its treatment appears at present to be well-founded.

Anesthetics

The past year has been highlighted throughout the world by numerous ether centennial meetings which have served as an impetus for various historical reviews dealing with ether and other anesthetic agents and methods (81 to 84).

During this period there has been a revival of interest in several long known drugs. A noteworthy example of this is the clinical use in anesthesiology of curare, a substance formerly used only for laboratory investigations because of its toxicity and uncertain composition. Curare is now available in a highly purified and standardized form (intocostrin) or in crystalline form (D-tubocurarine). These preparations have been widely accepted as valuable adjuncts for the production of muscular relaxation. Pathological changes produced in the laboratory animal by large single doses of curare have been described by Cole (85) while Smith *et al.* (86) have demonstrated its apparent lack of cerebral effects. Curare and curare-like compounds have been ably reviewed by Robbins and Lundy and are fully dealt with in a recent book by McIntyre (87). Certain problems that have arisen with the clinical use of curare are discussed by Hudon & Beaudoin (88). These include respiratory arrest by muscular paralysis, bronchospasm, laryngospasm, distension of the stomach, bronchial aspiration of fluids and hypotension. A synthetic curare substitute, myanesin [α,β-dihydroxy-γ-(2-methyl-phenoxy)-propane] has been introduced in England. Whereas the site of action of curare is at the myoneural junction, myanesin apparently exerts a depressant action on the reflex excitability of the spinal cord. It is claimed to give adequate muscular relaxation without respiratory paralysis (89, 90, 91).

Although trichloroethylene was synthesized by Fischer in 1864, and employed as an anesthetic by Striker and co-workers in 1935,

it had little clinical application until recently when its use in England has become rather popular, due to its nonexplosive properties (92, 93). This drug is also known as trilene. It should not be used to produce profound narcosis, or be given in a closed-circuit apparatus with soda-lime since products such as phosgene and dichloracetylene will be formed and produce toxic effects on the nervous system, as well as being highly explosive (94).

The present status of chloroform has been presented by Featherstone (95) who feels that there are safer alternative anesthetic drugs and methods. The laboratory and clinical investigators of chloroform at the University of Wisconsin are less discouraged about the potentialities of this drug (96).

The search goes on for a more perfect anesthetic agent. Two new inhalation agents isomeric with ethyl ether, namely N-propyl methyl ether (designated as metopryl) and isopropyl methyl ether (isopryl) have also been developed and given clinical trial by Krantz and his co-workers (97, 98, 99).

Robbins (100) has studied in mice the anesthetic activity of forty-six fluorinated hydrocarbons, and he has employed eighteen of these forty-six compounds in dogs. The results obtained with four of these compounds are such that further investigation of them is indicated.

There has been a recent revival of interest in the use of low spinal anesthesia in obstetrics, and numerous enthusiastic reports have appeared from widely scattered areas (101 to 110). New techniques in spinal anesthesia include differential spinal block as introduced by Sarnoff & Arrowood (111), and intraspinal segmental anesthesia as employed by Saklad and his co-workers (112). The new hypobaric tetracaine spinal anesthesia solution possesses some advantages according to the clinical experience of Lund & Rumball (113).

Studies have been made on the effect of pentothal on carbohydrate metabolism and on blood gases (114). The results indicate that in dogs the liver is severely taxed during prolonged pentothal anesthesia which may affect the normal functioning of the carbohydrate enzyme systems in the liver. A definite increase in the blood arterial oxygen was produced by adding oxygen or nitrous oxide-oxygen to pentothal anesthesia.

Experiments carried out to determine the alveolar and arterial oxygen contents during oropharyngeal oxygen therapy (115) show that, when properly employed, it is a very efficient method. More

recently Ohlsson (116) has made interesting investigations of oxygen toxicity at atmospheric pressure, while Haldane (117) reported the action of high-pressure oxygen on man.

Further studies of diffusion respiration have been made, with recovery of some dogs after a prolonged period of respiratory arrest (118). Radioactive sodium, fluorescence and oxygen have been used to determine the relative effects of various types of pulmonary resuscitation in dogs, and have revealed that mechanical resuscitators, using alternating positive and negative pressures, produce the greatest circulation (119).

Analgesics

A new analgesic, acetyl-5-bromosalicylic acid (bromoaspirin) was prepared by Krantz (120) and his associates, and administered to about three hundred persons. Their experimental and clinical evidence suggests that this drug is more potent and longer lasting in its effects than aspirin. The analgesic properties of trimethadione (3, 3, 5-trimethyl oxazolidine-2, 4-dione, tridione) have been investigated, and it is suggested that this drug deserves further clinical study (121). Scott & Chen (122) reported a pharmacologic study of a new analgesic substance 1, 1-diphenyl-1-(2-dimethylaminopropyl-2)-butanone, known as methadon, amidone, dolophine or 10820. This drug, originally developed in Germany, gives promise clinically of being a satisfactory substitute for morphine in the control of pain (123), causing less gastrointestinal distress, sedation, euphoria, and respiration depression. This drug may also prove of value in the treatment of morphine addiction since it can be satisfactorily substituted for morphine in addicts and later withdrawn without the appearance of withdrawal symptoms. Additional evidence that it does not possess addicting properties is shown by the fact that prolonged administration to monkeys resulted in increased susceptibility rather than tolerance (124). The introduction of this drug has put new life into the search for non-addicting morphine substitutes and new compounds of this type will undoubtedly be available for study in the near future.

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THE COAGULATION OF BLOOD

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This review covers the two-year period ending July 1, 1947, and is a continuation of the one published by Ferguson (1). An intervening article by Mulford (2) on plasma proteins covered certain articles which need not be cited in the present review. The subject of hemostasis is being reviewed in a special article of the current issue by Frantz. Articles on blood clotting which were published prior to July 1945 will be cited only when needed to supply background. From lack of space, articles of clinical interest will be cited only insofar as they illustrate important principles of physiology. Of special interest is a second edition of the monograph by Jorpes (3) on heparin. General reviews by Bethell *et al.* (4) and by Chargaff (5) and Astrup (6) should be consulted.

It is agreed that thrombin is derived from an inactive precursor, prothrombin, and that the conversion is furthered by the presence of thromboplastin and ionized calcium. The existence of a new accelerator factor is now recognized, and will be discussed later. This phase of clotting, the conversion phase, is followed by the clotting phase, during which the thrombin transforms fibrinogen into fibrin. Each of these two phases of clotting may be inhibited by heparin, acting in conjunction with one or more cofactors. This biphasic mechanism of clotting presumes the liberation of thromboplastin from cells and platelets as a preliminary step in clotting. This preliminary phase of clotting is now known to be of great importance; it will be discussed in the section on thromboplastin and platelets.

Thromboplastin and Platelets

It is widely held that thromboplastin is of at least two varieties. One is a thermostable fat-soluble type, made up apparently of cephalin, lecithin or other phospholipids. Another type is a thermolabile lipoprotein. Ferguson and co-workers (7, 8) claimed the existence of a third factor, differing from the other two. This is the proteolytic ferment of plasma, tryptase, which, in their opinion, serves in some ill-defined manner to convert prothrombin into

thrombin. This role of proteases and their additional role in the digestion of fibrinogen and fibrin will be discussed in the section on fibrinolysis.

Chargaff (9, 10) has continued his earlier work, showing that the lipoprotein variety of thromboplastin is composed of ultramicroscopic particles of sufficient size that they can be thrown down in the centrifuge at 31,000 *g*. He found that cell nuclei, isolated by the method of Dounce, have no thromboplastic activity.

Feissly (11, 12) has continued to develop the thesis that plasma contains a thermolabile type of thromboplastin, and he presented evidence that it is a lipoprotein. His experiments suggest that the presence of this material in plasma may be a contaminant liberated from platelets which are disrupted during collection and centrifugalization of the blood. At any rate, he found that this type of thromboplastin is present in platelets as well as in plasma. Also, he was able to show that platelets contain the lipoidal type of thromboplastin, but this latter type is not so readily set free from the platelet matrix.

There is excellent evidence that these various types of thromboplastin have special functional differences. It is well known that the lipoprotein derived from lung causes clotting of recalcified plasma very rapidly, while the fat-soluble variety, obtained by ether extraction of brain tissue, causes clotting far more slowly. The lipoid variety forms emulsions, whereas the lipoprotein forms a colloidal solution or an ultramicroscopic suspension. This difference in solubility has been thought to explain the difference in biological activity. More recently, evidence has begun to accumulate that the two or more types or components of thromboplastin are not alternative forms. It is held instead that they supplement each other. The complex nature of thromboplastin is suggested by the behavior of certain snake venoms. It has been known for many years that certain of these have powerful thromboplastic properties. Leathes & Mellanby (13) showed that lecithin augments this activity at least tenfold, whereas it augments the thromboplastic activity of brain extracts to a lesser degree. They regarded thromboplastin as an enzyme, and lecithin as a co-enzyme. Edsall (14) reported similar findings and showed that venom restores the action of thromboplastin which has been partially inactivated. Macfarlane, Trevan & Attwood (15) extended the earlier work

when they showed that prolonged centrifugalization at high speed (25,000 r.p.m.) removes lipoidal components from horse plasma, and this plasma, when subsequently recalcified, could no longer be coagulated by addition of the venom unless lecithin were also added. Quick also showed (16) the concurrent action of several varieties of thromboplastin by showing that the prothrombin time of human plasma, normally twelve seconds, may be reduced to the astoundingly low value of five seconds if lecithin and venom are used concurrently. Bertrand & Quivy (17) have recently made careful quantitative studies of the synergism which exists between venom and brain extracts. They employed various suboptimal amounts of venom and thromboplastin from brain and found that under certain conditions the combined effect of the two was more than a simple additive one. This "superadditive" effect supports the view that these two thromboplastic agents may have separate roles in the thromboplastic mechanism. Maltaner (18) has reported that some component of serum enhances the thromboplastic activity of cephalin. Finkelstein (19) has shown that thermostable and thermolabile varieties of thromboplastin differ in their reaction with "stored" plasma. Fantl & Nance (20) have reported that purified prothrombin is converted quite slowly into thrombin by thromboplastin alone, but more rapidly if a plasma factor is also present. This gave support to their previous observations (21) with whole plasma. Ware *et al.* (22, 23) have shown that such a factor precipitates at 0° by 40 per cent saturation with ammonium sulphate. They speak of it as an "accelerator factor."

This accelerator factor may be identical to a plasma factor previously described by Owren (24, 25), and characterized more carefully in another article (26). His work centered about a very instructive human bleeder. In this patient there was evidently a congenital deficiency in thromboplastic activity. The "prothrombin time" was prolonged, but could be brought back into normal range by addition of a component of normal plasma, this factor being a component of thromboplastin, and not prothrombin itself. He concluded that this component acts to reinforce the thromboplastin employed in the prothrombin test. He speaks of it as a fifth factor of clotting, i.e., factor V. It is to be hoped, that in the future all cases of "idiopathic hypoprothrombinemia" will be given special study to determine whether the missing factor is really prothrombin or whether it is the factor V of Owren.

Since platelets contain thromboplastin of at least two types, the question of platelet stability is of great importance. The importance of water-wettable surfaces has a long and interesting history. It has been known that such surfaces bring about the rupture of platelets. Bordet maintained, in addition, that such surfaces bring about the formation of prothrombin (serozyme) from an inactive precursor (proserozyme). This conclusion did not receive wide acceptance. Recently Tocantins (27, 28, 29) has reexamined the role of water-wettable surfaces in promoting clotting, and has concluded that they absorb inhibitory substances from plasma. These substances are thought to play an important role in hemophilia.

For many years, investigators have employed a coating of parrafin on tubes and syringes, in order to minimize the effects of water-wettable surfaces. In this way it has been possible to secure avian plasma which does not clot unless thromboplastin is added. In mammalian blood, the platelets are more readily disrupted and the technical results have been disappointing. The recent discovery by Jaques *et al.* (30) that the treatment of needles and glassware with silicone minimizes the mechanical rupture of platelets, provides the investigator with a technic which promises to be of the greatest importance. With this technic it has been found possible to obtain stable mammalian plasma, comparable to the avian plasma secured with the aid of paraffin.

Brinkhous (31) in a preliminary report, presented a new viewpoint regarding the disruption of platelets. His work showed that plasma contains a factor which brings about the dissolution of platelets after blood is shed. It would appear that this lysis of platelets liberates the thromboplastin which causes conversion of prothrombin into thrombin. It appears that the lysis of platelets does not occur in hemophilic blood, for the reason that the lytic factor of plasma is absent. Brinkhous found that in normal blood this lytic action is retarded if the blood is collected in silicone-treated glassware. From this it would appear that normal plasma contains the lytic factor in an inactive form, but the mechanism by which it is activated is still unknown.

The views on hemophilia presented by workers at the Boston City Hospital also postulate the existence of an unidentified plasma factor. It is conceivable, of course, that the factor might correspond to one of the components of thromboplastin already described.

They maintain that in some way the factor enters directly into the clotting mechanism and is not concerned in any way with platelets. This concept is difficult to reconcile with the experiments of Brinkhous, for his experiments did point to deficiency in a platelet lysin. It is possible, of course, that there is a deficiency both in a platelet lysin and in some other plasma factor which is still unidentified. Recent work from this clinic is that of Minot & Taylor (32).

The effects of administering thromboplastin intravenously vary according to dosage, speed of injection and type of thromboplastin. Baker, Noran & Larson (33) reported that homologous extracts are more toxic than heterologous ones. The former, in small doses, produces capillary thrombi in the brain, similar to those sometimes seen in human cases of encephalitis associated with pneumonia. Copley (34) claimed that thromboplastin given intravenously is effective in combatting peptone shock, and Feigen & Deuel (35) reported that thromboplastin may have therapeutic value in burn shock.

It has long been known that a water-soluble material can be extracted from placental tissue, and that this material is highly toxic when injected intravenously. This fact has been thought to be significant in explaining the toxemias of pregnancy. Schneider has published a number of papers dealing with the characteristics of this toxic substance, and has now concluded (36) that it is thromboplastin. As with other varieties of thromboplastin [Moulonguet *et al.* (37)], the animals can be protected against the toxic effect by prior administration of heparin. It remains to be seen whether heparin will also protect against the toxemias of pregnancy.

Macht (38) and De Takats *et al.* (39) presented additional data showing that digitalis causes the clotting time in rabbits to be shortened. Moldavsky and co-workers (40) and Askey & Neurath (41), Werch (42) and Villegas (43) reported similar findings, and this has been confirmed by Macht (44) for streptomycin as well as for penicillin. He (38, 45) has also found that mercurial diuretics cause acceleration of the clotting time. In most of this work it has been assumed that the drugs in question possess thromboplastic powers, though it is recognized that they may act indirectly by reinforcing the activity of one or more of the thromboplastic components or even by accelerating the disruption of platelets. Finally,

they may inactivate the natural inhibitors of clotting. Regardless of the theoretical explanation, these findings may be of clinical importance for purely practical reasons, in relation to thrombosis and embolism.

It is well known that thrombi are formed either by coagulation of the blood within vessels, or by agglutination of platelets (platelet thrombi), or by a combination of the two mechanisms. The role of platelets is thus quite important, and variations in number, in health and disease, have received renewed attention by Aggeler and co-workers (46). Day (47) has made further study of the tonicity test for platelet stability. Wright (48) has devised a test for variations in the adhesiveness of platelets. The test showed that anticoagulants cause a decrease in adhesiveness of platelets. A reduction in adhesiveness of platelets was observed (49) in animals treated with dicoumarol, and this would seem to imply a close relationship to the prothrombin level, though one might also suspect a reduction of the platelet lysin of Brinkhous. Wright (50) also found increased adhesiveness of platelets following parturition and after surgical operations. It would seem that this method might give valuable evidence of incipient thrombosis, thus permitting the clinician to be more selective in the use of anticoagulant therapy.

Prothrombin and Thrombin

Seegers *et al.* (51) made electrophoretic studies on highly purified prothrombin (1,200 units per milligram dry weight) and found the material to be 80 per cent homogeneous. According to Deutsch (52) certain fractions obtained by the cold alcohol technic of Cohn contain eighty-five units of prothrombin per milligram. Ferry & Morrison (53) reported that their thrombin had an activity of ten to fifteen units per milligram of protein. Robbins (54, 55) published immunological and other data on a preparation obtained by simple isoelectric precipitation of plasma. It is evident that neither Deutsch, Ferry & Morrison nor Robbins have obtained products more than 10 per cent pure, as judged by the standards of Seegers. With such products, it is impossible to decide whether the properties noted belong to prothrombin or to the 90 per cent protein impurities. It is disappointing to see energy deployed on products so inferior to those of Seegers. Seegers *et al.* (56) have made quantitative studies on the adsorption of thrombin

by fibrin. The interesting observation was made (57) that the digestion of fibrin by fibrinolysin liberates the adsorbed thrombin.

It has been known for several years that when plasma is stored in the "blood bank" for a number of days, the prothrombin titer decreases gradually. Several years ago, Quick (58, 59) suggested that plasma contains two types of prothrombin. The labile type, which disappears from stored blood, was termed prothrombin A; the type which disappears on administration of dicoumarol was spoken of as prothrombin B. The B-component is readily removed from plasma with adsorbents; the A-component is not. On mixing the A-deficient plasma in suitable proportions with B-deficient plasma, the prothrombin time of the mixture was found to be normal or nearly so. The mechanism by which joint action of the two components is secured was not clarified; obviously they reinforce each other but are not merely additive. Munro & Munro (60) studied the prothrombin time with various proportions of the two types of plasma and found that complex relations prevail. Munro *et al.* (61) reported that both components fall following hepatectomy.

The view that prothrombin is made up of two components has not received universal acceptance. The prior experiments of Lavergne (62) and the recent experiments of Loomis & Seegers (63) and of Ware *et al.* (64) have led these authors to conclude that the fibrinogen undergoes denaturation, during storage, and that the lengthening of the prothrombin time is due to this. These views would seem to eliminate the need for assuming the existence of two types of prothrombin. Quick (59), however, has presented a rebuttal, and Deutsch & Gerarde (65) agree with him. In the meantime, additional workers have accepted the concept of two types of prothrombin. Among these are Oneal & Lam (66) and Zondek & Finkelstein (67). Obviously, the problem cannot be regarded as being settled and it may well be that prothrombin A will prove to be identical to factor V of Owren or to the accelerator factor of Fantl & Nance (20) and of Ware *et al.* (22, 23).

It is thus a question as to whether the labile factor is really a form of prothrombin or whether it is an accelerator of prothrombin conversion. Obviously, the accelerator factor offers a complication in the assay of prothrombin, but this will be discussed in a later section. The anomalous observation of Banfi (68) that pro-

thrombin rises during the early stages of storage may be the result of existing uncertainties in the assay of prothrombin.

Vitamin K.—It is well established that the plasma prothrombin level falls in states of vitamin K deficiency. Ferraro & Roizin (69) have published extensive data on the resulting anatomical lesions. In recent years, little of interest has been reported regarding the faulty absorption of the vitamin in obstructive jaundice or in disease of the intestinal tract. The fall in prothrombin level, usually occurring during the first few days of life, is well recognized, as is the low level sometimes present immediately at birth. The actual effect of these changes on mortality rate involves the statistical analysis of a large number of cases. Schmitz (70) reports a new clinical series. Waddell & Whitehead (71) reported 3,775 treated infants and 2,879 cases in which the vitamin was given prepartum to the mothers. The mortality of treated and untreated cases was the same. Potter (72) studied 13,190 cases, in which one-half of the mothers had received vitamin K prepartum. The fetal and infant mortality rates of the treated series was 29.8 per 1,000; that of the untreated controls was 25.8 per 1,000. These reports are in keeping with the common opinion that bleeding from the alimentary tract or from external foci is not a common cause of death. Intracranial hemorrhage is an important cause of death, however, but these series would seem to imply that prothrombin deficiency is not a major cause of intracranial hemorrhage. Potter's series (72) included fatal cases of intracranial hemorrhage, both in treated and untreated cases. It is unfortunate that the vitamin was given for such a brief period prior to delivery. Had it been given for several days, it is possible that intracranial hemorrhage incident to delivery might have been reduced in the treated series.

In this same connection, it has been held that retinal hemorrhage in the newborn may indicate a serious deficiency in vitamin K. Falls & Jurow (73) report that neither antepartum nor intrapartum administration of the vitamin has any effect in reducing the incidence of retinal hemorrhage. These authors suggest that trauma and anoxia are the important factors in the production of this type of hemorrhage. Wille (74) also discounted the relationship of K-deficiency to retinal hemorrhage.

Quick (75, 76) was unable to confirm an earlier thesis that large doses of vitamin K bring about an elevation of the prothrombin

level. In fact, there is now considerable literature on the toxicity of vitamin K. It has been studied by Richards & Shapiro (77). In mice, the lethal dose of vitamin K was found to be 250 mg. per kilo. In dogs, the lethal dose was 100 to 150 mg. per kilo. Continued administration of sublethal doses produced an anemia which disappeared on withdrawal of the drug. The various toxic doses here reported are 500 to 5,000 times as great as those ordinarily used in man.

In disease states, the "toxic" dose of vitamin K may be less than under normal conditions. Shapiro & Richards (78) found that in certain cases of biliary disease, the prothrombin level was higher without vitamin K therapy than with it. Richards & Shapiro (77) reported a case of idiopathic hypoprothrombinemia. Large doses of vitamin K (190 mg.) were given to correct a bleeding tendency manifested by menorrhagia, ecchymoses and nosebleed. Following vitamin K administration, the prothrombin level actually decreased. Later, Hauser (79) reported an instance of familial vitamin K-resistant hypoprothrombinemia. Two sons and the father had a hypoprothrombinemia, with definite hemorrhagic tendency in one of the sons. The parents were consanguineous. Vitamin K administration to the sons intensified the hypoprothrombinemia. Still later, Quick (80) described a congenital hypoprothrombinemia involving one son, the mother and a sister. The father and two brothers had normal levels. The sister had severe menorrhagia. Quick states that vitamin K at first appeared to control the bleeding but later did not. The effect of vitamin K on the prothrombin level was not specifically recorded. In Owren's case (26), the administration of vitamin K did not affect the prothrombin time. In his case, there was a deficiency of the factor V, not of prothrombin. The same may be true of other cases of congenital "hypoprothrombinemia."

The mechanism by which vitamin K serves in the production of prothrombin remains obscure. Berger *et al.* (81) injected radioactive vitamin and found rapid diffusion into the blood. There was no evidence of fixation by the liver, however.

Dicoumarol.—The literature on dicoumarol is now quite extensive. Mentzer and co-workers (82) made additional reports on the chemistry of dicoumarol and related compounds. The clinical work on thrombosis continues to favor the therapeutic use of heparin or dicoumarol. An extensive study was reported by Zil-

liacus (83). Additional papers may be listed at this point: Allen *et al.* (84), Allen (85), Askey & Neurath (41), Barker and co-workers (86), Bauer (87), Bouvrain (88), Evans & Boller (89), Facquet and co-workers (90), Jorpes (3), Link (91), Meyer (92), LeFevre (93), Segard (94), Bruzelius (95), Wright (96, 97, 98), Nichol & Page (99), Parker & Barker (100), Glueck (101), Loewe & Hirsch (102), Loewe *et al.* (103), Peters *et al.* (104). Wright (105) pointed out that dicoumarol neither complicates the course of a patient with coronary occlusion, nor affects the rhythm or rate of the heart; nor does it alter the progressive changes of infarction, once it has occurred. He believed the value of this therapy to be in preventing propagation of a thrombus already present, as well as the additional formation of thrombi. His survey (105) indicates that, in the absence of anticoagulant therapy, 20 to 37 per cent of patients with myocardial infarction eventually have emboli or subsequent thrombosis. Ogura *et al.* (106) gave data on the Waugh & Ruddick test indicating the need for anticoagulants in coronary thrombosis. Wakim and co-workers (107) said that thyroid extract has no effect on the action of dicoumarol.

From the experimental point of view, Quick (108) reported that the chick is highly refractory to dicoumarol. Rigdon *et al.* (109) reported that ducks deficient in vitamin A are abnormally sensitive. Field (110) induced a hypoprothrombinemia in suckling rats by feeding dicoumarol to their mothers. On the fourth day the pups had petechiae, and after five or six days they developed other types of hemorrhage. Addition of vitamin K to the mothers afforded a greater protective effect to the suckling pups than to the mothers. Quick (111) also administered dicoumarol to a bitch before parturition and found that the pups had a greater hypoprothrombinemia than the mother. Vitamin K administered to the pups failed to show a marked effect on the hypoprothrombinemia. He confirmed Field's work showing that dicoumarol passes over into the milk.

Bose (112) found the thromboplastic activity of brain tissue reduced in animals which have been treated with dicoumarol. Stefanini & Blanchaer (113) confirmed this. In perfusion experiments on rats, Lupton (114) presented evidence that the liver of dicoumarol rats is unable to manufacture prothrombin. The amount formed normally during perfusion is small, however.

Eriksen *et al.* (115) synthesized a hydroxy derivative of dicoumarol. Intravenous doses to rabbits (12 to 120 mg.) had an anticoagulant activity reaching a maximum 6 to 8 hours after injection,

in contrast to the interval of 24 to 48 hours with dicoumarol itself. The anticoagulant activity of this new compound was thought to result not only from a hypoprothrombinemia, but likewise from the occurrence of a substance in the plasma inhibiting the first stage of the clotting process, i.e., the formation of thrombin from prothrombin. The evidence for the inhibition consisted in an observed discrepancy between the relation of calcium ion concentration and clotting time of blood from hydroxy-coumarol-treated animal as compared to a normal. Additional studies [Jacobsen & Plum (116)] on this inhibiting substance indicated that it was not heparin; it is stable, dialyzable, and its effect is dependent upon its absolute concentration rather than the prothrombin content.

Because of the antihemorrhagic activity of phthalic acid and derivatives in bile-ligated rats, Jaques & Dunlop (117, 118) gave this drug to dogs two days after administration of dicoumarol. Small doses did not change the prothrombin time. Single large doses (40 mg. per kilo) followed by a continuous injection of 10 to 30 mg. per kilo did change the prothrombin time from eighty seconds to forty-five seconds.

It has often been suggested that dicoumarol plays the role of a vitamin K antagonist. A report by Davidson and co-workers (119) presented further evidence on the apparent antogonism between these two substances. Smith *et al.* (120, 121) and Meunier and co-workers (122) found that certain substituted napthoquinones also appeared to be vitamin K antagonistic. Irish & Jaques (123) studied the effect of dicoumarol on the plasma fibrinogen. They found that small intravenous doses (10 to 12 mg. per kilo) cause a hyperfibrinogenemia; large doses (18 to 20 mg. per kilo) cause a fall. They suggested that dicoumarol may be toxic to the liver.

Several years ago, Link and his associates pointed out that salicylates also cause a lowering of the prothrombin level and suggested that dicoumarol might act by the liberation of salicylates through decomposition. Recent work, both experimental and clinical [Butt *et al.* (124), Conte-Marotta & Postiglione (125), Coombs *et al.* (126), Rapoport & Guest (127), Owen & Bradford (128), Zimmerman & Shapiro (129), Clausen & Jager (130), Neivert (131), Nitshe *et al.* (132), and De Vita & Fazio (133)] has confirmed the deleterious action of salicylates, though Coombs *et al.* (126) and Lüdin (134) hold that the dosage commonly employed in clinical medicine in not within the danger zone.

Mentzer *et al.* (82) synthesized a number of derivatives of

dicoumarol. The substitution of one hydroxyl group with monacetyl, monopropionyl and monobutyl groups did not reduce the anticoagulant activity. Huebner & Link (135, 136) made additional studies on the chemistry of hydroxycoumarin [see also Bose *et al.* (137)].

Effect of other substances.—Somewhat less evident is the mechanism of hypoprothrombinemia reported from the use of quinine [Pirk & Engelberg (138)] and of indandione derivatives [Kabat and co-workers (139)]. Quick (75, 76), however, was unable to demonstrate the effect of quinine. It seems probable that differences in method of assay of prothrombin are responsible for the discrepancy.

Macht (38, 140) and Werch (42) have shown that drugs of the digitalis group cause acceleration of clotting, and this raises the point as to whether the use of these drugs in heart diesase might aggravate the existing tendency toward thrombosis and embolism. Macht assumed that the drugs in question acted as thromboplastic agents, though specific tests for thromboplastin were not reported. Although Sokoloff & Ferrer (141), Cotlove & Vorzimer (142) and Poindexter & Meyers (143) disputed these findings, De Takats *et al.* (39) and De Vita & Fazio (133) confirmed them and reported that the prothrombin levels tend to rise above normal values when digitalis is administered. They also showed that clotting of the blood is not as readily retarded with heparin as normal (heparin tolerance test). These findings suggest that the effect of digitalis may be complex, and that factors in addition to prothrombin may be involved [see also Villegas (43), Ramsey and co-workers (144), Moses (145), and De Vita & Fazio (133)].

Even more controversial is the role of the methylated xanthines. Certain of them, such as aminophylline, are employed as vasodilators in cases of coronary occlusion. It has been claimed for many years that these drugs cause acceleration of the whole blood clotting time, and this is now confirmed by Field *et al.* (146, 147) and by Scherf (148), both of whom report an increase in the prothrombin level. Other reports [Quick (75, 108), Dey *et al.* (149), Rieben (150), Gilbert and co-workers (151), Breytspraak & Greenspan (152), and Nitshe *et al.* (132)] fail to obtain these results. The apparent discrepancy probably lies in uncertainties of methods for assay of prothrombin.

Also, of uncertain mechanism is the reported role of penicillin

and streptomycin in reducing the clotting time [Macht (44), Dixon (153), and Moldavsky and co-workers (40)]. Lewis (154) failed to obtain this effect with penicillin. Certain mercurial diuretics are said to promote clotting [Macht (45)].

The Assay of Prothrombin

The past decade has seen much controversy regarding methods for the assay of prothrombin. Some of the discussion has centered about minor technical details, but much of it has dealt with the underlying principles and their validity. The various one-stage technics are based upon mixing thromboplastin with plasma [Quick *et al.* (155)], or whole blood [Ziffren *et al.* (156, 157)], and noting the clotting time. This clotting time varies normally between six and thirty seconds, depending upon the animal species studied and upon the type of thromboplastin employed. The mechanism of the test is rather complex, consisting as it does of two overlapping reactions. The first reaction consists in the conversion of prothrombin into thrombin; the second is concerned with the reaction between the thrombin and fibrinogen, with resultant formation of fibrin. Evidence indicates that the thrombin titer rises gradually during the test interval, and that clotting occurs by the time 10 to 20 per cent of the prothrombin has been converted into thrombin. Thus, the test is a measure of the speed with which the thrombin titer can be built up to the clotting level. Obviously, this speed depends upon the amount of prothrombin present, and Quick has insisted for several years that this is the only significant factor.

The two-stage technic, historically the older [Warner *et al.* (158, 159), Smith *et al.* (160)], separates the conversion phase from the clotting phase. In the first step, the thromboplastin is allowed to react with the prothrombin until the conversion reaction is complete. In the second stage, purified fibrinogen is added in order to ascertain the amount of thrombin formed during the first stage. Under many circumstances, the one-stage methods are in close agreement with the two-stage methods, but under other conditions they consistently differ as much as 100 per cent. When these discrepancies were first noted [Warner *et al.* (161), Ziffren *et al.* (156), Owen *et al.* (162), and Smith (163)], it was pointed out that variations in conversion rate could create striking errors in the one-stage results. The two-stage technic, on the other hand, provides as much time as may be needed for conversion, and is largely inde-

pendent of conversion rate. Independent evidence gave added support to the view that variable conversion renders the one-stage technic unreliable in certain cases. The recent work of Owren (24, 25, 26), Fantl & Nance (20, 21), and Ware *et al.* (23), already mentioned, gives direct evidence for the existence of an accelerator factor. The factor can be separated from prothrombin and thromboplastin. Though in crude form, this factor can be shown to increase the rate at which thromboplastin converts prothrombin into thrombin.

It must be admitted that the one-stage methods have many advantages of technical simplicity, but the criticisms already noted have now been re-emphasized by Nitshe and co-workers (132) and by Rieben (150). It is to be hoped that ways will be found to stabilize the accelerator factor during the test, and thus render the method more specific for prothrombin. There is little reason to believe that the two-stage titer of plasma is affected by the accelerator factor, but obviously further studies are needed.

We wish to refer again to the unsolved problem of prothrombin A and prothrombin B. If two types of prothrombin do actually exist, this fact must be taken into account in the assay. The matter is even more complex if one adopts the suggestion of Zondek & Finkelstein (67) that there exist A and B types of thromboplastin, comparable to A and B types of prothrombin. It may be, however, that the new concepts regarding the accelerator factor will clarify these various suggestions, with simplification of theory.

Somewhat less fundamental, nevertheless quite important, are some of the proposed modifications in technic. Jaques (164), Rieben (150), and Owren (26) have modified the two-stage technic. Like the earlier workers, Herbert (165) and Stewart (166), both Jaques and Rieben have employed constant dilution in place of variable dilution. It is of interest that Irish *et al.* (167), using this method, found the conversion time of prothrombin to be reduced in experimental shock. Sternberger (168) used alcohol in his two-stage procedure in order to inhibit antithrombin.

Numerous modifications of the one-stage method of Quick have been proposed, though few have met with the approval of Doctor Quick himself. Several of the modifications deal with preparation or storage of the thromboplastin used in the test. Aggeler (169) has conducted extensive studies along these lines, and Kazal and co-workers (170, 171, 172) have advocated the use of antioxidants

and antiseptics. Lein & Hays (173) have also advocated the use of hydroquinone. Martin *et al.* (174) has studied a number of variables. Banfi & Tanturi (175) have constructed a nomogram for calculation of prothrombin.

Considerable controversy centers about the merits of diluting the plasma prior to assay. The proponents point out that the contour of the clotting time curve is such that very little precision can be expected with high-titer plasma, unless the dilution technic is used. Quick (75), who originally devised the dilution technic [Quick & Grossman (176)], now objects to its use on the somewhat vague grounds that the "physical-chemical equilibrium is profoundly disturbed." Aggeler *et al.* (169) makes extensive use of dilution curves which are carefully prepared for individual cases. Nitshe and co-workers (132) and Rapoport (177) have found that the "constants" for the dilution curve formula vary in an unexplained manner. Nitshe *et al.* also advocated dilution with purified fibrinogen solution. Rosenfield & Tuft (178) and Tanturi & Banfi (179) diluted with plasma from which prothrombin has been adsorbed. Fisher (180) preferred the plasma methods to the whole blood methods. He does not dilute. Gerber & Blanchard (181) discussed the role of colloids in the assay procedure. Long (182) discussed the effect of heparinization on the prothrombin time.

Several reports [Stefanini & Blanchaer (113), Martin *et al.* (174), Jaques & Dunlop (183), Kleinman *et al.* (184), Owren (26), and Rocha e Silva & Andrade (185)] indicated the importance of controlling the calcium level in the assay procedure. It is agreed that errors otherwise arise, especially when the prothrombin titer is low. DeBeer (186), Page (187) and Reitz (188) have accepted the use of Russell viper venom as a substitute for thromboplastin in the one-stage test. Rocha e Silva & Andrade (185) decided against the use of venom. Honorato (189) uses bubbles to determine the endpoint of clotting.

Fibrinogen and Fibrin

Ferry & Morrison (53) and Ferry *et al.* (190) prepared fibrinogen which was 45 to 60 per cent pure, and were able to secure information regarding the size and shape of the molecule. Other physical properties were also recorded. A later report [Ferry and co-workers (191)] included studies on factors which influence the structure and rate of formation of fibrin clots.

Mommaerts (192, 193) and Van der Meer (194) studied factors which inhibit the formation of fibrin. Mommaerts believes that fibrin formation is a two-step process, the intermediate product being "profibrin." At a certain zone in the acid range, profibrin can be formed, but fibrin does not make its appearance until neutrality is restored.

Morrison (195) reported finding several types of fibrinogen. One which separates out on cooling has striking effect on the sedimentation rate. Owren (26) concluded that the fraction which separates out is really a profibrin.

Field & Dam (196) reported that diet has an effect on the fibrinogen level in the plasma. Field *et al.* (147) reported that certain methylated xanthines cause increase in the level of fibrinogen in the plasma. A number of cases of congenital deficiency in fibrinogen, either partial or complete, have been reported [Pinniger & Prunty (197), Henderson and co-workers (198), Jeanneret & Rutishauser (199), Yaeger *et al.* (200) and Freeman and co-workers (201)].

Fibrinolysis

It is now agreed that fibrinolytic ferment may be formed from an inactive precursor normally present in plasma. This proferment can be activated by chloroform, or by material formed by certain strains of streptococci. It was originally thought that this bacterial product was a fibrinolysin in its own right, and this term is still applied to it by some workers. It is to be hoped that the terminology recently proposed by Loomis, George & Ryder (202) will be adopted. They refer to the bacterial agent as streptokinase. The proferment of plasma, sometimes spoken of as "plasmin," is designated as profibrinolysin. The term fibrinolysin is reserved for the fully activated enzyme. Inhibitors normally present in plasma are referred to as antifibrinolysin and antiprofibrinolysin. The ferment itself has been purified by Loomis & Smith (203).

Ferguson *et al.* (7, 8) tend to identify the fibrinolytic enzyme with other proteolytic enzymes (tryptase, serum protease), and they assign a thromboplastic role to such enzymes. Kaplan (204), on the other hand, has reported that trypsinogen and profibrinolysin each have their own specific activators which are not identical. This was taken to imply that fibrinolysis and serum protease are not identical. Seegers & Loomis (205), using purified fibrinoly-

sin, found that it does not clot oxalated plasma or fibrinogen. Like Glazko (206), they found that it does not inactivate thrombin. They did report, however, that it inactivates prothrombin [see also Seegers (57)]. Loomis & Smith (203) report that the fibrinolytic ferment splits fibrinogen as well as fibrin, forming at least two recognizable components, the α and β-fractions, apparently like those previously described by Seegers (207) in the case of simple autolysis. The purified ferment did not cause clotting of fibrinogen, however. Fibrinolytic preparations which do cause clotting are probably contaminated with thrombin.

Reports from the Commission on Acute Respiratory Diseases (208) show that the antifibrinolysin titer is commonly elevated in patients infected with the β-hemolytic streptococcus. Macfarlane & Pilling (209) made studies on antifibrinolysin. Kaplan (210, 211) reported that certain species have high titers normally. Guest *et al.* (212) also found the inhibitors high in bovine and guinea pig blood, low in the blood of chickens and cold-blooded animals, but intermediate in man, dog, and rat.

The activation of profibrinolysin by chloroform is obviously an artificial procedure. Nor is fibrinolysis confined to cases in which the hemolytic streptococcus is involved. Macfarlane & Biggs (213) studied the the relationship between fibrinolysis and operative procedures. Biggs, Macfarlane & Pilling (214) found that blood taken during and after exercise or after injection of epinephrine shows an increased tendency toward fibrinolysis, and this is not associated with coincident changes in the leukocyte count. Nor is it evident whether this represents a change in profibrinolysin level in the blood or whether it represents increased activation of profibrinolysin already present. Smith & Smith (215) reported that menstrual fluid as well as venous serum during menstruation contains fibrinolysin.

A large literature is accumulating on the relationships between protease activity, fibrinolysis, and shock, but these fields lie largely outside the scope of this review. For leading articles, the reader is referred to Ungar (216) and to Tagnon *et al.* (217 to 220), Lewis *et al.* (221), Rocha e Silva *et al.* (222 to 225), and Wells *et al.* (226).

The Natural Inhibitors of Blood Clotting

Normal plasma contains a "natural antithrombin" which can cause inactivation of thrombin. If heparin is added, the anti-

thrombic titer is increased enormously. This increase results from the combined action of heparin and the heparin co-factor of plasma. It is possible that this newly formed antithrombin is basically similar to the "natural antithrombin" already present, merely differing in having a larger content of heparin.

Heparin also has a role in blocking the formation of thrombin. Howell held originally that it did so by uniting with prothrombin and blocking its conversion. Since then, others have held that it combines with thromboplastin, thus preventing the formation of thrombin. It has not been possible to decide between these two competing theories; in fact, several years ago, Brinkhous *et al.* (227) showed that heparin cannot block the formation of thrombin unless a heparin co-factor is present, but it was not ascertained whether this co-factor is the same as the one concerned in the inactivation of thrombin.

From all of the work in this field, it would thus appear that the mechanisms of action of heparin and the co-factor(s) are complex. It seems unlikely that this problem will be solved until it becomes possible to secure pure prothrombin, thromboplastin and co-factor(s), all in adequate amounts for study by modern methods of protein chemistry. The recent papers by Honorato *et al.* (228) and Feissly & Enowicz (229) provide additional data regarding the role of heparin, but they do not elucidate the fundamental chemical mechanisms.

Regarding the structural chemistry of heparin, it has become evident that the material, as prepared at present, is a mixture of compounds which differ in their degree of sulphonation, and perhaps in other regards also. Wolfrom & Karabinos (230) were unable to obtain any sugar derivatives other than d-glucosamine and a uronic acid. Wolfrom & McNeely (231) found evidence that the heparin activity may center in the N-bond, not in the sulphate groups. Work from this same laboratory [Wolfrom *et al.* (232)] contradicts the older view of the Toronto group that heparin potency varies with the species from which it is isolated. They suggest that the variations in potency are to be ascribed instead to the sensitivity of the crystalline barium acid salt and the ease with which it is inactivated by mild acidity.

New work [Grönwall *et al.* (233), Astrup & Piper (234, 235), and Piper (236, 237)] has extended the older studies on a group of compounds having biological properties similar to those of heparin.

Some of them are almost as potent, but many are toxic. Clinical use of heparin is held back by the costly methods of production. If an inexpensive substitute of nontoxic character could be discovered, it would fulfill an important need.

Jalling *et al.* (238) do not approve the use of oxalated plasma in the assay of heparin, for recalcification is a part of the procedure, and this introduces variations in the amounts of calcium, and this in turn has a marked effect upon the proteins involved. They prefer to conduct the assay with whole blood, and they describe a detailed procedure for doing this. The error is thought to be in the neighborhood of 5 per cent.

Bertrand & Quivy (239) discuss the use of Fisher's formula in the assay of anticoagulants, and they demonstrate that a decrease in prothrombin has an effect quite different from that produced by an excess of anticoagulants. Trethewie (240) has perfused pneumonic lungs and has reported upon the anticoagulant properties of the perfusate. Rocha e Silva (225) has perfused the liver, and has suggested that platelets and leukocytes play a role in the liberation of heparin into the perfusate. Hermann, Galloni & Cier (241, 242) presented evidence that heparin is formed or stored in the reticuloendothelial system. Their discussion neglects recent publications concerning the role of mast cells in the storage of heparin. Schürer (243) made histological studies and found storage of heparin by certain large basophilic cells of the serosae, as well as by the ordinary mast cells. These observations are of interest, but the authors should not speak loosely of storage by "reticuloendothelium," for these basophilic cells are included in the reticuloendothelial system only by courtesy. No evidence was presented to show that storage occurs in the macrophages, the Kupffer cells or in other major cell types included within this system.

Allen & Jacobson (244) and Allen (245) found that exposure of the entire body to ionizing irradiation increases the heparin content of the blood. The tendency to bleed is due to this as well as to the well-known decrease in platelets. Toluidine blue, an antagonist of heparin, may be a useful therapeutic agent.

Gerendas (246) found that the antithrombic titer gradually falls in blood stored in the refrigerator. It is not clear, however, whether the fall involves the heparin content or whether it involves the content of the heparin co-factor.

Selsø (247) heated plasma to 56° C. and found that the stability

of the co-factor could be increased by the addition of heparin. Macfarlane (248) and Tagnon & Soulier (220) have found that the soybean trypsin inhibitor delays coagulation, but the mechanism of action is evidently somewhat complex.

Honorato & Amo (249) and Honorato & Hache (250) reported that a choline-deficient diet causes a rise in the antithrombic titer. Presumably, this implies an increase in heparin, for it can be counteracted with protamine. They believe, furthermore, that the prolongation in prothrombin time in vitamin K deficiency is related to an increase in the amount of antithrombin present, a view widely at variance with current concepts. Glasson & Kunz (251) found the antithrombic titer to be low after surgical operations; it is said to be high in hypertension. Feissly (252), Munro (253) and Pavlovsky (254) agree with Tocantins (27) that an inhibitor is present in the blood of hemophilic patients. Quick *et al.* (255) found that heparin does not prevent the fall in platelet count seen in peptone shock.

Miscellaneous

Tocantins (256) has made an interesting effort to bring together the various factors concerned in hemostasis, and to give the proper relative weight to such factors as vascular contraction, agglutination of platelets and the laying down of fibrin. Bertrand & Quivy (257, 258) have studied the influence of temperature on coagulation and have discussed the existence of a critical point.

Field *et al.* (259) have presented data on a family of hemophilic dogs. The hereditary pattern as well as the clotting tests showed close similarity to those of the human disorder. Perkins (260) and Estren *et al.* (261) have discussed pseudohemophilia. Levy (262) has described a family of non-hemophilic hereditary hemorrhagic diatheses. These clinical reports should be read in the original.

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HEMOSTASIS[1]

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In the chapters on Blood, Blood Cytology and Blood Coagulation which have appeared since 1942 in the Annual Review of Physiology, it will be seen that the references on hemostasis are few in number. They represent, however, two new concepts, and hence two new techniques in surgery, i.e., the acceleration of clotting by local application of thrombin preparations, and the staunching of hemorrhage by tamponnade, a time-honoured method, but now modified by the advent of preparations which can be left with impunity in the closed wound to be absorbed.

For extensive bibliography on blood clotting, reference is made to articles in this Review by Smith (1), Bruner (2), Quick (3), Johnson *et al.* (4) Ferguson (5), Mulford (6) and in this volume Smith *et al.* (7). Hemostasis ultimately depends upon coagulation of blood. Tamponnade in a wound is ineffective unless clots finally form sealing the defects in the bleeding vessels. Contraction of vessels, as another factor in cessation of blood flow has been studied by MacFarlane (8) in reference to capillaries. Substances in blood serum and platelets which stimulate smooth muscle and might, in consequence, influence the caliber of larger vessels, and hence the escape of blood, are reported by Zucker *et al.* (9, 10).

Aids proposed for hemostasis in wounds are the direct outcome of the study of blood fractions. Following the isolation of prothrombin from beef serum by Seegers *et al.* in 1938 (11), a series of studies was reported on the isolation and preparation not only of beef thrombin by Seegers *et al* (12 to 15, 17, 18) and Milstone (16) but by Parfentjev *et al.* on the isolation and preparation of rabbit thrombin (19, 20) and of human thrombin developed in the laboratory of the Department of Biochemistry, Harvard University (21, 45 to 50). Thromboplastin from pigs' lungs reported by Howell (22) and given to hemophilic pigs, reduced clotting time as did the human lung product in a single case. Robbins (23) found the antigens in thrombase species specific.

Thrombin.—Beef thrombin used as a hemostatic spray in ex-

[1] This review covers the period from May, 1938 to August, 1947.

perimental animals was reported in 1939 by Seegers *et al.* (24) and clinical studies in various fields of surgery rapidly followed (25 to 40), including studies on the antigenicity (41). Rabbit thrombin used in clinical cases was reported early also (42, 43, 44).

Fibrin and fibrin plastics.—Human fibrin foam and film were developed at the same time as human thrombin, and as the foam was designed primarily as a carrier of thrombin, the experimental studies (21, 45 to 50, 53) were rapidly followed by the clinical application in neurosurgery by Ingraham *et al.* (51 to 55) and Woodhall (56); in oral surgery by Losch (57); in prostatic surgery by Quinby *et al.* (58); and in general surgery by Bailey *et al.* (59) and Fallon *et al.* (60). Beef thrombin already having had ample clinical trial was sometimes used in conjunction with human fibrin foam. Coagulum contact methods reported by Sano (61, 62, 63), Clark *et al.* (64), McEvitt (65) and Cronkite *et al.* (66); and plasma-thrombin clot and "suture" reported by Young *et al.* (67, 68), together with films as surface dressings for burns (69, 70), are developments of these blood fractions which, although not designed primarily for the control of hemorrhage, do however seal oozing surfaces and in burns presumably lessen fluid loss.

Gelatin sponge.—The expensive and somewhat unreliable source of human fibrin sponge stimulated the research for a substitute. Correll & Wise (71, 72) devised a gelatin sponge which was found in animal studies to be absorbable and nonirritating by Light (73, 74), Jenkins *et al.* (75, 76) and MacDonald & Matthews (77). Clinical studies with gelatin sponge and thrombin by various investigators followed (74, 76, 78, 79, 80), the largest series being neurosurgical reported by Pilcher (78). There was no evidence in the clinical series that the gelatin had antigenic properties, and from the standpoint of uniformity of the product, availability for large scale production, texture, tensile strength and ease of handling in surgery, it was superior to fibrin foam. In early reports gelatin sponge was used as a carrier of thrombin (75 to 80) but in later experimental work (81, 82, 83) it was used for the most part without the enzyme.

Oxidized cellulose.—Oxidized cellulose, the first chemical report of which appeared in 1942 by Kenyon and his associates (84, 85, 86), was studied immunologically by Heidelberger & Hobby (87) and Kabat *et al.* (88) because it was proposed as a blood substitute. With knowledge of these studies, the second of which had not yet

been published, Frantz (89) undertook experimental studies of tissue reactions to oxidized cellulose in the form of cotton, paper and gauze. Simultaneously, Putman (90) reported seventeen clinical cases in which oxidized cotton had been used as a carrier of thrombin in neurosurgery. The specific hemostatic action of oxidized cellulose was noted in experimental studies by Frantz, Clarke & Lattes (91), and considered to be the result of the combination of the cellulosic acid with hemoglobin, and possibly with serum proteins thus forming a black, sticky mass filling the crevices of the wound space. This "styptic" action of the acid gauze and cotton deserves further study. It renders the use of thrombin unnecessary, the hemostatic action of the gauze and cotton being more effective when they are used dry. Since there was some evidence that the acidity of the gauze was high enough to render thrombin less effective (92, 93) this specific hemostatic action was a fortunate and unexpected finding. A comparative study of the addition of antibiotics to gelatin sponge and oxidized cellulose (93) showed the former compatible with both penicillin and streptomycin, while the acidity of oxidized cellulose was detrimental to penicillin. Further experimental studies in tissue reactions were undertaken by Gruhzit *et al.* (94), Frantz (91, 95), Burns (96) and by Anderson & McIntyre (97).

Clinical studies of the use of oxidized gauze or cotton in general and special fields of surgery followed (98 to 116). There has been no demonstration of antigenic properties in clinical cases (105). Many of these studies, experimental and clinical, were comparative with fibrin foam, gelatin sponge, and oxidized cellulose (52, 73, 76, 77, 80, 81, 82, 93, 95, 105, 112, 113, 115). In earlier studies, chiefly because of Putnam's preliminary report (90), oxidized cellulose was used in conjunction with thrombin; later the hemostatic packing was used dry.

An inexpensive, rapid test method for the large number of substances proposed as possible absorbable packing was devised by Lattes (117) and consists of a technique for the aseptic implantation of the material to be tested in the subcutaneous tissues of the back of rats. So far only human fibrin sponge, gelatin sponge, and oxidized cellulose have proved to be safe and useful and therefore have been made available commercially.

Alginates and other substances.—A synthetic adhesive proposed for treatment of wounds of liver is not absorbable and the oxidation

suggested to make it so has not yet been reported (118). Starch sponges proposed by Bice *et al.* (119) were submitted to Frantz for study under OSRD contract, and were found to be irritating. A casein sponge (120, 121), said to be absorbable, was not submitted to this reviewer for comparative tests.

Because commercial production of a uniform preparation of oxidized cellulose presented certain engineering problems which rendered the cost high, and because none of the three absorbable hemostatic materials in clinical use was sufficiently stable to withstand sterilization by autoclave, a naturally occurring organic acid which was closely related structurally to cellulosic acid (oxidized cellulose) was investigated. This was alginic acid, derived from seaweed. It was found by Blaine (122) to be absorbable as was anticipated and it could be autoclaved. Further studies by Frantz (123), however, showed it to have less specific hemostatic effect than oxidized cellulose and to be slightly more irritating in the tissues of rats and dogs than the oxidized cellulose. The possible hazard of its clinical application, however, was strongly emphasized by Chenoweth (124) who found in pharmacological studies of various preparations, that they were highly toxic for cats. Before these studies appeared, limited clinical application was reported in bleeding tooth sockets (125). Only small amounts were used here and were, therefore, probably within the limits of safety.

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PHYSIOLOGICAL PSYCHOLOGY[1]

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War, which accentuates activities in many lines, has had a disturbing effect on the progress of science. Although stimulating applications of known principles, it delays research by diminishing the number of people in the laboratories and by diverting the attention of those who remain. This seems to have been true more in this country than in some others, notably in Russia, where the value of theoretical science has been recognized for many years.

As most of the laboratories in the U. S. A. concerned with physiological psychology have been occupied with war problems, it will be several years before normal productivity is apparent in published works. This is understandable when one considers the length of time for scientific "reconversion" plus the lag between research and publication. A letter from a leader in the field illustrates.

> I was taken out of physiological psychology during the War years, and in the past year and a half, I have been busy in human experimental work of no particular interest to the area of your present review.

In spite of huge sums of money donated to research by the Government, the confusion of reorganization has not contributed to the progress of Science.

In a field so indefinite as "physiological psychology" the included material depends largely on the point of view of the writer. It may be helpful to the reader in knowing what bias to expect to state that my interest is predominantly in the biological principles that influence behavior colored chiefly by an experience with the Pavlovian methodology and human psychopathology.[2]

Anatomical Localization

The role of the subcortical and segmental nervous system in mammals remains unsettled. It has been known for two decades from the researches in Pavlov's laboratories (Zeliony *et al.*) that a

[1] The period covered in this review extends from January, 1946 to July, 1947.

[2] For assistance in abstracting the material from journals I am indebted to Miss Ursula Traugott of Wellesley College.

primitive type of motor conditional reflex could be formed without the cortex but Pavlov was inclined to minimize this effect in the light of his failure to form salivary conditional reflexes (crs) without the cortex. Both Pavlov (1) and Lashley (2) asserted on experimental grounds, though from different viewpoints, that the conditional reflex (cr) function was widely spread over the whole cortex. Recently, carefully performed and controlled experimentation by Bromiley (3) in Bard's laboratory confirms the findings of Zeliony and shows that differentiation is also possible. Although these facts do not negate the role of the cortex as the chief organ of cr formation, the exact site of this formation is an open question. Previous work of Brogden & Gantt (4) that crs could be formed to cerebellar reflexes, and the work of Löwenbach & Gantt (5) and Spiegel (6) that crs can be formed to vestibular reactions give added evidence that the site of the cr formation might be extended.

In the past year a lively discussion has taken place between Shurrager (7) and Kellogg (8) concerning the question of crs in a spinal dog. By an ingenious technique, Shurrager showed that muscle fibers innervated by a single motor neuron in isolated spinal cords can become conditioned in an acute experiment: "Individual motor cells are shown to possess independent ability to learn."

Kellogg and co-workers repeating Shurrager's experiments in a chronic dog with complete transection of the spinal cord found that although the hind limbs of four dogs could be conditioned before transection, there was no evidence of a conditioned movement of the limb after transection. There was, however, a slight muscle twitch and a crossed extension reflex which Kellogg considers equivalent to what Shurrager described as a conditional reflex (cr). No evidence was seen of retention of either the preoperative or postoperative crs. Kellogg thinks that the muscle twitch could be elicited to a strong conditional stimulus (cs) per se, and that the twitch is a component of the startle pattern. Summation of stimuli or reflex sensitization would explain the phenomenon. Shurrager claims that in acute dogs the spinal cr could be extinguished and reestablished in animals that lived as long as three days. Kellogg reasons that if his healthy animals could not form spinal conditional reflexes (crs) it is less likely that one would see it in an acute preparation.[3]

[3] For recent work concerning spinal reflexes in transected cord lesions of the human being, see Macht (9).

The work of Woolsey (10), Talbot (11), and others in showing dual afferent areas in the cerebral cortex for the visual and auditory sensory systems provides an electrophysiological basis for the existence of crs after the extensive cortical extirpations of Pavlov and others.

The cerebral cortex was shown by Bromiley to be unnecessary for the formation of specific motor crs in a decorticate dog surviving thirty-three months. The dog lifted his hind paw to both auditory and visual conditional stimuli. Extinction was possible. Sham rage and emotional disturbances were frequent. Histological examination revealed no neocortex on either side except minute fragments of gyrus proreus, of the insula and of the limbic fields. "On both sides the putamen is severely damaged, nucleus caudatus and amygdala are almost intact."

In another study on the effect of cortical ablation to the responding leg Bromiley (12) states:

> Unilaterally decorticate cats, trained in a shock avoidance conditioned response situation with the unconditioned stimulus applied to the leg contralateral to the ablation, tend to give conditioned responses of the unshocked leg. When trained with the shock applied contralateral to the intact hemisphere, the responses are of the shocked leg as is the case with normal cats trained by the same technique.
>
> Preparations with one frontal pole ablated behave as do the hemidecorticates; those with one occipital pole ablated, however, give normal responses. Some animals with somatic sensory area I or II removed on one side responded like normal animals. Others with these ablations gave a number of conditioned responses of the unshocked leg, but not to the extent shown by hemidecorticate or frontal pole preparations and, in the course of training, they finally responded with the shocked leg only.

Destroying three bilateral cerebral cutaneous areas (Woolsey's cutaneous area I foreleg, trunk and arm, Woolsey's area I for face, Woolsey's cutaneous area II), Allen (13) found that the third lesion especially was concerned with correct inhibition of the foreleg motor cr.

Mettler and colleagues (14) showed that removal of the corpus striatum without cortical ablation produce dullness, disorientation without withdrawal from pain.

The relation of the cortex to speech and sensation [Rasmussen Penfield (15)] was studied by electrical stimulation of the human cortex in 206 operations under local anesthesia.

> Sensory responses for the extremities were contralateral, but in the face area 10 per cent of the stimulations resulted in bilateral or ipsilateral sensation. These

points were all situated in the anticipated sensory sequence and frequently were adjacent to loci producing the usual contralateral responses pertaining to that part. . . . Furthermore, intraabdominal sensation is localized at the lower end of the precentral gyrus, below the area for mouth and throat. The extent of this representation into the fissure of Sylvius and on to Island of Reil has not yet been determined.

Section of the corpus callosum and commissura anterior by Ades & Raab (16) showed a failure of bilateral coordination, more pronounced in the absence of area 4. Compensation was rapid. "The rostral half of the collosum seems to be the only portion involved since the effects of total section are no greater than those of section of the rostral half." There was no effect on motor behavior by section of the commissura anterior.

In the human being the role of the corpus callosum and commissura has been studied by Smith (17). Epileptics in whom the commissural pathways were divided by operation were followed for eighteen months. Although Kinnier Wilson had believed that there is no syndrome of the corpus callosum, and Bykov in Pavlov's Laboratory demonstrated no impairment of function in dogs except that of differentiation of tactile stimuli on symmetrical sides of the body, the usual neurological concept has been that the dominant cortex (left in right-handed people) controls the other through the fibers traversing the corpus callosum and that the subordinate hemisphere is under inhibitory control in regard to learned reactions. In the patients in whom the corpus callosum, the anterior commissura and the hippocampal commissura were severed, there was no change in laterality (handedness, eyedness and footedness). Pavlov and Lashley have both shown experimentally the ability of the cortex to compensate and take over a function generally considered as dependent on restricted areas. Smith concludes that there is no justification for the clinical belief in the principles of "action and localization so often attributed to the fibers of the corpus callosum on the basis of clinical observations." He believes that there is integration of activity and unification of function providing for organization of postural activity and transient responses, a concept of multiple integration.

Kennard (18), in an interesting review of the effect of emotions on striate muscle, describes the anatomical basis for these autonomic relationships with the somatic nervous system.

Lashley (19) has made an important further contribution to his analogy of the action of the cortex by separating the chief

functional areas of the rat's cortex by incisions along their margins symmetrical in the two hemispheres. He found that:

> Separation of each adjacent pair of architectonic fields was followed by normal performance in some cases. Detailed analysis of the lesions indicates that, when deterioration occurred, it was due to the interruption of thalamo-cortical fibers or to the destruction of cortical tissue. There was no evidence of additional effects ascribable to the interruption of transcortical connections.

Removal of the motor area by Yakovleva (20) or of the parietal lobe was found to modify the latent period of the conditional response.

The role of the sensory and motor cortical projections were studied by Whatmore & Kleitman (21) in escape and avoidance conditioning.

> Hemidecortication had no effect on escape conditioning but caused complete abolition of that avoidance response for which the cortical projection of the unconditional stimulus had been removed. Extension of the lesion to include the sensori-motor cortex of the remaining hemisphere still did not impair performance of the escape response. It was concluded that in avoidance conditioning, the cortical projection of the unconditional stimulus occupies an important position in the neural pathways activated by the conditional stimulus and that in escape conditioning there is no localized cortical structure necessary for elicitation of the acquired response.

As the result of a separate study, Kleitman, Morgan & Whatmore (22) conclude that avoidance conditioning when carried out concurrently with nonavoidance conditioning has a deleterious effect on the nonavoidance conditioning but is itself fully retained.

The role of the cortex and midbrain (colliculi) in retention and formation of acoustic conditional reflexes (crs) has been studied by Raab & Ades (23). Total bilateral extirpation of the auditory cortex in cats required retraining for crs previously learned, but after bilateral destruction of the superior and inferior colliculi the crs were retained perfectly; in the absence of both cortex and colliculi differentiation suffered. The authors conclude that in the intact animal the conditional reflex is cortically mediated but that there are three functional levels—cortical, midbrain, and bulbar.

The role of the optic cortex in the retention of crs to visual stimuli was investigated by Wing (24, 25). He found that a conditioned leg flexion to light is retained after removal of both areae striatae but with loss of differentiation and that this could be restored by training. These experiments are in general in conformity to what had been previously shown by Pavlov (1).

The great advocate in this country of frontal lobotomy, Freeman (26), has recently applied the method for the relief of intractable pain, such as that of tabes dorsalis, and inoperable cancer; lobotomy alters the individual's reaction to pain without changing his ability to feel pain, thus making it bearable. Watts & Freeman find themselves in agreement with Wolff in the distinction between the perception of pain and the reaction to it (27).

A more extensive operation, prefrontal lobectomy, was shown by Morgan & Weiner to reduce audiogenic seizures in rats by 54 per cent (28).

A psychological study of the effect of lobectomy and lobotomy has been carried out by Walker (29), and by Bucy, Halstead & Carmichael (30). They found that, although the former operation grossly impaired the biological intelligence, prefrontal lobotomy was without this effect; they state: "Little is known concerning the behavioral effects of prefrontal lobotomy."

The Conditional Reflex

Work by the methodology of the cr has been carried on chiefly in Russia, where it was initiated by Pavlov, and later in the United States. Since Pavlov's death in 1936, to the best of my knowledge, there have been four general trends.

One of these is represented by clinical work in the schools of Bechterev and Ivanov-Smolensky with motor conditioning and of Krasnogorski with salivary conditioning in children. Interesting correlations have been made between the results in the human and those found by Pavlov in dogs. Krasnogorski has worked chiefly with pathological children and infants, and Ivanov-Smolensky with adolescents. A wealth of data has been accumulated, but perhaps the interpretations have suffered from too slavishly adhering to those given by Pavlov in the dog. Greater progress might have been possible if there had been new and original imaginative forces.

Studies inspired by Pavlov's ideas have been continued by a number of his pupils. In spite of some interesting amplifications this work too has been handicapped by the lack of new developments. Much of it is repetitive and descriptive with sterile interpretations on the basis of Pavlovian induction, irradiation, etc.

Two special forces for development exist in the schools of Anochin (31) in Moscow and of Bykov (32) in Leningrad. The former

has many novel and varied experiments in neurophysiology on the interaction of the periphery and the centers. These have been recently elaborated in this country by Sperry (33).

Since the time of John B. Watson, and other pioneers such as Yerkes and Lashley, there has been a slow growth of the work in this country. Some retardation and reaction unfortunately followed the brilliant experiments of Watson on account of the strict limitation of his concepts. Besides two or three laboratories devoted almost entirely to developing this field and methodology, there are many workers, mostly psychologists, who employ the method and are responsible for an extension of the concepts [Lashley (2, 19), Hull (34), Hilgard & Marquis (35)]. In addition to the worthwhile researches there are a number of papers purporting to revise or criticize Pavlovian concepts which are valueless because the writers show a lack of knowledge as well as understanding of even the available works of Pavlov which have been translated into English. A very few physiologists [Bard (36), Kleitman (21), Allen (13)] employ the method occasionally for anatomical or other special research. Perhaps the greatest development, or at least the most spectacular, in this country has come from those in the field of psychopathology who have been studying experimental neuroses in various animals (Liddell those in the sheep, goat, dog and pig; Masserman those in the cat; Maier and Morgan those in the rat, and Gantt those in the dog). A few clinicians are developing the method along special lines (Gantt in the examination of children and psychotics, Voegtlin, Kindwall and others as a means of treating alcoholics).

Continuing his work on shock therapy, Gellhorn (37) has shown that in the rat insulin coma acts only on inhibitory crs, restoring them, without effect on the excitatory crs. He explains the restoration of inhibitory conditional reflexes as due to increased hypothalamic discharges to the cortex, making subsequent threshold cortical processes supramaximal.

Magnesium deficiency in rats has proven effective in producing convulsions to auditory stimuli but Patton & Lezovik (38) showed that a combination of sound with light shock and rotation is ineffective in producing the seizures.

Lashley & Wade in discussing the Pavlovian theory of generalization (39) state that it is built upon two fundamental postulates (*a*) the association of the unconditional reflex with the con-

ditional reflex, and (*b*) the irradiation of the effects of training with one stimulus to produce association with similar stimuli; but that both postulates are contrary to fact. Hull (40) questions the above arguments and states that

> their belief in the absurdity of attempting to reduce the habit strength and reaction potential resulting from learning to mathematical treatment in the form of quantitative equations, ironically comes at the moment when this seems actually to be taking place.

Podkopaev (41) adds to Pavlov's excitatory and inhibitory factors in the cortex a third neutral one, deduced from his study of the relationships between the conditional reflex and the unconditional reflex.

Conditional response of invertebrates.—Although the great entomologist Fabre doubted the ability of insects to make learned individual responses, the formation of crs has recently been demonstrated by Bertholf in bees to visual stimuli (42), by Dallenbach in the cockroach (43), and by Piéron (44) in the snail *Lymnea stagnalis* (withdrawal into the shell). The rate of extinction in the latter animal decreased as the temperature increased from 8° to 26°C.

Conditional response in old age.—Apter and Gantt in Baltimore and Pavlova (45) in Russia have studied the effect of age and senility on crs. In old age the weaker forms of crs such as trace and delayed crs were formed with difficulty or not at all, with some decrease in salivary crs and a relative increase of salivary unconditional reflexes (URs), indicating a greater effect of senility on the more predominantly cortical reactions than on the subcortical.

The relation of intensity of cr to intensity of cs and unconditional stimulus (US) was studied by Fyoderov (46) in which he showed that the cr is stronger when the US is presented rapidly than if it is presented slowly. Frequent presentation of the cs tends to decrease the magnitude of the cr.

Mowrer & Lamoreaux (47) conclude on experimental grounds that in avoidance conditioning the cr and the unconditional response resemble each other or differ depending upon whether the cs and the US call for the same or different responses; where the primary drive is a noxious one, the secondary drive (underlying the cr) is the state of fear, and the response which eliminates one will eliminate the other. Fear itself being a product of learning cannot legitimately be used as a basis for explaining further learning.

The latent period of the salivary cr was shown by Otterback & Gantt (48) to be an accurate measure of intensity of the food cr, for in contrast to the latent period of the motor component of the food cr, which is unreliable:

Using 12 and 2 grams of food the LPs were 1.9 and 2.5 seconds respectively, the crs 389 and 306, and the URs 992 and 484 cu. mm. On the other hand, with a *constant* amount of food (US), the daily variations of secretory LP showed a much smaller correlation with fluctuations of the cr.

The latent period of the cr is also a characteristic of the individual as well as of the conditions of experimentation.

A comparison of the electroencephalogram with a defense cr in the rabbit by Livanov & Poliakov (49) showed that an increase in frequency of electroencephalographic waves accompanied the appearance of the cr. At trial 50 but not after the cr had become established, whenever electroencephalographic activity of one half the frequency of the stimulus (a rhythmic one of 3 per second), the respiratory rate approximated that of the electroencephalographic waves.

Subsequently it was shown that sound, pain, and other stimuli which elicited the defense reflex also produced the brain wave pattern, as did spontaneous movements which duplicated the cr. Finally it was shown that these rhythms disappeared with the development of differentiation, somnolent states, and in extinction.

On the basis of these results, the authors suggest that conditioning the defense reaction to a flickering stimulus is dependent on the production in the cortex of periodic changes in the excitability of the motor areas.

The Pavlovian methodology is not only important as an objective technique, but because it is opening up a whole new field for investigation. The progress of physiology has been along two lines: the study of isolated organs and tissues and even separate cells ("more and more about less and less"); and the newer physiology of the entire intact organism. The latter is the field to which Pavlov devoted himself experimentally. Much theoretical discussion has also been directed to this aspect of physiology, for example the philosophical concepts of Smuts with his "holism" and of Adolf Meyer with his "holergasias." Many others who write of "the organism as a whole" or of "dynamisms" should also be considered in this field, although some of them either through intolerance or

lack of understanding of the experimental method consider themselves in opposition to the Pavlovian concepts.[4]

The new trend in physiology is away from the nineteenth century idea that it was possible to construct a physiology of the entire organism as a sum of the individual organs, tissues and cells. Bykov in a recent Russian book (50), points out that, although with so exhaustively studied a drug as epinephrine, we know little about the role of epinephrine secretion by the suprarenal glands in the active life of the organism.

> The views held on the subject are contradictory, beginning with an almost complete denial of any role played by adrenalin in normal physiology (Gley, Stuart, Rogov) and ending with its being considered as a factor which almost determines the behavior of the human (Cannon). Yet of all the hormones adrenalin seems to have been best studied both biochemically and physiologically.

Concerning the spinal cord we are familiar with its function after extirpation of the medulla, cerebellum and cerebrum (Goltz, Sherrington, Magnus, Bard). Yet we do not know the physiology of the spinal cord in the intact organism, when impulses arise in the brain, nor the interaction with the higher centers.[5]

Bykov has shown the interaction of the nervous system with the kidneys, the liver, the cardiorespiratory system, the gastrointestinal tract, the metabolism, the thermal regulation, the individual tissue processes, through the cr connections. In the present review it is not possible to describe the work in each one of these fields, but as an example may be mentioned the investigation of the cr connections of the kidneys. Although the mechanism of renal secretion has been exhaustively studied with respect to composition of the blood, blood pressure, water intake, its relation to the higher nervous processes has not been determined, in spite of its dependance upon nervous control. Dogs with externalized ureteral orifices were kept on a constant diet and observed for a number of years. Spontaneous secretion varied with either excitatory or inhibitory nerve processes, for example, the presence of the investigator. Owing to the action of such extraneous agents, exclusion in a Pavlovian camera was essential. Bykov states

> the method of the chronic experiment demands that the investigator should be

[4] There is no attempt on my part to deny the need for constant revision of concepts and of new experimental work.

[5] The recent researches of Woolsey and others in electrophysiology are providing one approach to this problem.

specially trained as it greatly differs from the acute experiment in which the investigator considers only one aspect of the process and is isolating a complex phenomenon. With the chronic experiment the complex process is observed as it runs its natural physiological course.

In the chronic experiment it is possible to study the most complex functional phenomenon. The knowledge of the complex adjustments of the organism can only be gained in the chronic experiment in a sound and intact animal. Neither artificial nerve stimulation nor the extirpation method can give a true idea of a complex functional phenomenon.

As an unconditional stimulus (US), the injection of 100 cc. of water by rectum was used. Later diuresis began when the dog was placed in the stand. Although formation of the conditional diuresis occurred on the second day, extinction of the conditional diuresis was very slow as compared with extinction of a salivary conditional response. This is parallel to what Gantt (51) has found with extinction of the cardiac conditional response, in that it is much more difficult to extinguish than either the salivary or the motor. The conditional diuresis could also be formed to a tone as well as to the milieu. Secondary conditional reflexes could also be formed.

Anuria was produced by a painful stimulus (faradic current) to the hind leg; this could be used as the unconditional stimulus for an inhibitory conditional reflex (as shown by Orbeli). That the kidney is very sensitive to cortical stimulation may be deduced from the speed of the formation of conditional reflexes of the first and second order, both excitatory and inhibitory. Indifferent external agents such as sounds, lights and odors, unless they are very strong, fail to produce an effect on diuresis.

Pituitrin, which inhibits the secretion of urine when water is injected into the stomach, could be employed as the unconditional stimulus for an inhibitory conditional stimulus.

Bykov's ingenious analysis of the mechanism of conditional reflex formation to the kidney gives a clear insight into a complex obscure function. After denervation (completed by decapsulation) of the kidneys the conditional reflexes were found to persist. His analysis was carried out in the following way: depending on the state of the humoral milieu it was possible to form either an excitatory or inhibitory conditional reflex. Both a hormonal and a nerve control contributed to the conditional reflex formation: in an animal hypophysectomized by the ring method of Speransky (52)

and having also one kidney denervated and decapsulated and the other kidney with normal nerve connections, it was possible to obtain conditional reflexes in the latter kidney but not in the former—the nerve pathways are presumably from the cortex through many synapses to subcortical ganglia, diencephalon, sympathetic cells in the spinal cord, and probably through the splanchnics to the kidney; the neurohumoral pathway is from the cortex to the hypophysis or pigments of the infundibulum causing a secretion of pituitrin. The mechanism of the action of the hypophysis on diuresis is still not clear—whether it is through tubular reabsorption or glomerular filtration is uncertain.

Not only with the kidney but with the spleen there is shown to be a conditional reflex activity (contractions) by a double pathway—through the splanchnic nerves and through the secretion of epinephrine. Differentiation between two metronome rates in the splenic response could be established.

Using thyroxine as an unconditional stimulus changing basal metabolism (increased oxygen consumption), it was possible to form a conditional reflex to a signal. In thyroidectomized animals no conditional reflex to basal metabolism could be formed, whereas in conditional reflex changes in chemical thermoregulation the thyroid is not the only means for transmitting impulses from the cerebral cortex; the paths over which the impulses are conveyed from the cortex to the tissues depend upon the nature of the unconditional stimulus. As shown by Gantt (53) the same reaction can or cannot be conditioned depending upon whether it is produced by central or isolated peripheral excitation, for example gastric and salivary secretions when they accompany the central state of hunger can be made into conditional reflexes but not when they are produced by stimulation of the peripheral nerves as by histamin and pilocarpin.

Cardiac conditional reflexes have been studied by Gantt and co-workers [Hoffman, Dworkin, Robinson (51, 54)]. That cardiac changes accompany emotional states has been axiomatic from time immemorial. Recently Liddell and Gantt have shown the existence of cardiac variations in neuroses. Gantt and collaborators have demonstrated a specific cardiac conditional reflex on the basis of both excitation and inhibition, to food and to painful stimuli. Gantt & Hoffman showed that the cardiac conditional reflex was proportional to the intensity of the unconditional stimulus

(amount of food) as well as to the temperament of the dog. Phlegmatic and older dogs showed less change in heart rate and variability seemed to be related to stability of the individual.

The use of the cardiac conditional reflex has led to certain interesting observations and conclusions which would not have been possible without its study. Thus Robinson & Gantt (54) were able to establish a conditioning of sexual excitation through the cardiac component; previously it had not been possible to demonstrate in the laboratory the specific motor component of sexual conditional reflexes. This was probably owing to the complexity and peculiarities of sexual excitation, for clinical and everyday observations testify to the role of sexual excitation in behavior.

The heart rate provides a useful adjunct to the study of what had been briefly described by Pavlov as the orienting, investigatory, or focusing reflex, but to which there has been devoted no special study outside of three papers from Pavlov's laboratories. The orienting reflex is an inborn reflex, however of a much more complicated nature than is the startle reflex, which has been thoroughly studied (Moro, Hunt, Landis, Slight). While the orienting reflex had been described previously by its motor aspects, the inclusion of the cardiac component has enabled Robinson & Gantt (54) to follow the transformation of a new stimulus on repetition into a neutral agent and by reinforcement into conditional stimulus.

Although the orienting reflex (investigatory or questioning reaction) has motor, respiratory and cardiac components, the latter is the most definite and the most constant. The orienting reflex was characterized by directed muscular movements, and by respiratory, salivary, and cardiac reactions, which were present even in dogs deprived of most of the cortex. The cardiac is the most easily evaluated of all these reactions. The orienting reflex disappears in most individuals (both dog and human) after several or more repetitions of the neutral stimulus; its persistence, a sign of hyperreactivity, is seen in both animals and patients.

There is a general parallel between the cardiac, salivary, motor and respiratory components, the cardiac and salivary being the most definite and sensitive. Robinson & Gantt conclude the heart rate is a measure to a far greater extent of central nervous excitation than the less significant phenomena (movement and secretion). As Hoffmann & Gantt (51) have shown in dogs and White-

horn *et al.* (55) in patients the heart rate goes up before rather than during a movement such as a shift in position.

A comparison of the cardiac conditional reflex with the salivary and motor conditional reflexes in the same dogs reveals that the cardiac conditional reflex, although formed more quickly than the salivary or motor, is generally more difficult to extinguish and more stable than these other components. Thus there appears to be a natural physiological cleavage in the organism among different functions. The external movements of adaptation, executed through the skeletal musculature and the cerebrospinal nerves, although not formed as soon as the cardiac reactions, are easily inhibited when the environment changes, but the visceral reactions represented by the heart rate, may persist for years after the external situation no longer demands activity. We have hence the picture of an animal conforming in its external aspects while internally it is as much or more violently agitated than it was in the situation calling for action.

Gantt concludes from his work with the cardiac conditional reflexes that there is a normal physiological basis for maladaptation and even conflict. First even in conditional reflexes demanding little or no physiological or external activity, such as to the sound of a metronome symbolizing only 1 gm. of food, there is a marked over-activity of the visceral system and especially of the heart; the heart rate increases out of all proportion to the physiological need. Secondly the heart, this vital organ for the maintenance of the life and health of every living tissue every moment, does not adapt harmoniously compared with the muscular and digestive systems, and may even show an increased activity in a situation to which the organism has long since made adaptation in its external activity.

That life exists at all is a tribute to its power for adaptability, so beautifully evident in homeostasis (Claude Bernard, Cannon), in the preciseness of gastric secretion [Pavlov (56)] and salivary secretion [Gantt (51)], and even in the intake of food [Richter (57)]. Nevertheless the living organism wages a losing battle (though prolonged) ending in death. On the psychobiological level we see the basis of this failure to adapt in the lack of harmony between the circulatory mechanism, this phylogenetic veteran of the physiological systems, and the other systems of the body. Dysfunction, reaching into the highest cortical levels, is not a

recently acquired characteristic, but probably as old as life itself.

This cleavage has been recognized by the philosopher[6] but, in the wake of the nineteenth century adolescent science, it is overlooked by the modern scientist. It is now time that we admit the physiological basis of dysfunction as of equal importance with the function of adaptability.

A cardiac time reflex has been demonstrated by Gantt (59). At two-minute intervals dogs were given a conditional stimulus (cs) every other cs being accompanied by a shock to the paw, for twenty repetitions daily. Thus the dog had a regular alternation of excitatory and inhibitory conditional stimuli (csi). The heart rate not only increased to the excitatory cs but during several seconds before the cs, i.e., every four minutes. The average of thirty readings was: control during interval, 107; ten to five seconds before excitatory tone, 124; five to zero seconds before excitatory tone, 128; cardiac conditional reflex (cr) during three seconds action of tone, 142; cardiac unconditional reflex (UR) during shock, 138. For the inhibitory tone changes in heart rate were small: control, 109; five to zero seconds before inhibitory tone, 111; during three seconds action of inhibitory tone, 115. Whether such visceral changes provide a basis for the estimation of time by the organism still has to be determined.

The importance of time not only as a basis for conditioning but in the formation of the experimental neurosis has been demonstrated by Liddell (60). He states:

> In any sheep or goat picked at random from the flock we get tonic immobility with 2 minute intervals between signals and chronic agitation with 5, 6 or 7 minute intervals between the recurring 10 second positive signals. The animal tolerates shock alone at any of these intervals. The shocks have to be associated with the 10 second signals to precipitate the experimental neurosis.

If an animal is free to run and if signals and shocks are administered at regular intervals "it makes its own Pavlov frame, i.e., it gives up running to the signal and behaves as if it were in an actual Pavlov frame." Liddell thinks in terms of tempo (fast or slow) and extent (diffuse or focused) rather than in terms of reward

[6] "Good," as Aldous Huxley reflects in *Eyeless in Gaza* (1936), "is what makes for unity. . . . Evil is the accentuation of division. Pride, hatred, anger—the essentially evil sentiments . . . because they are all intensifications of separateness." "Since separateness is the condition of individual life, evil is inherent in reality on the human level" (58).

and punishment. In line with Liddell's production of spasticity in goats as a result of experimental conflict is the attempt of McGill & Welch (61) to explain hysteria as a conditional reflex, on the basis of Pavlov's concept of hysteria (62).

Stead & Hickam (63) have investigated the effect of anxiety on the cardiac output. Twenty-three unselected medical students were studied by ballistocardiograph immediately before and then twenty-four hours after an important academic examination. In the anxious state cardiac output increased 50 per cent over the composed level, the heart rate 30 per cent, and blood pressure 15 per cent, with lower peripheral resistance. Individuals showed wide variations.

Hospital patients, some with cardiovascular disease, were studied by intracardiac catheterization, and the cardiac output by the Fick method. Anxiety was spontaneous or induced by suggestion; relative composure by reassurance or light sedation. Anxious individuals at rest may have a cardiac output much in excess of that of composed patients but without a corresponding increase in oxygen consumption. Exercise in anxious subjects may even decrease the cardiac output below the resting state. This observation runs parallel to that of Gantt in dogs and of Whitehorn in patients—that some patients have a slower heart rate when reading. It also shows an index of variability which is less when the animal is being stimulated, e.g., during the action of the conditional stimulus, than it is during the intervals of no external stimulation. Possibly the relatively mild external stimulus is a weaker stimulus than are the internal stimuli arising spontaneously in the disturbed organism.

Vasomotor responses were conditioned to a visual stimulus in four of ten human subjects, a faradic shock being used as an unconditional stimulus. The vascular reactions were measured by a photoelectric plethysmograph. The vasomotor conditional reflexes were stable, those subjects showing autonomic instability were more easily conditioned (64).

The employment of the cardiac conditional reflex by Woolsey & Gantt (unpublished work) in two dogs in which one cerebral hemisphere and part of the mesial portion of the other had been removed indicates that the formation and differentiation of cardiac crs proceeds almost as readily as in normal animals. Hence it may be concluded that at least some control of the cardiac conditional

reflexes lies in that part of the cortex which remained in these two animals or that its mechanism is chiefly subcortical.

The clinical study of motor crs has been carried out by Fleischmann, Fleck & Gantt (65). In hypothyroidism the ability to form crs was directly proportional to the basal metabolic rate and inversely proportional to the blood cholesterol concentration but not to mental function as measured by the Binet-Simon Test. Within a few weeks after thyroid therapy in a cretin, age 13, the basal metabolic rate changed from −36 to +32, the blood cholesterol concentration from 571 to 212, the cr function from 20 to 90, while the IQ remained at 81 per cent. Although the motor cr is a relatively crude indicator, compared to other cr measures, it is closely related to certain metabolic functions and is thus a more reliable and sensitive indicator than are the conventional mental tests. Cr function depends upon the *status praesens* while the Binet-Simon depends chiefly upon the accumulation of reactions to a fairly standardized environment.

Psychiatric patients with anxiety were shown by Welch & Kubis (66) to form psychogalvanic crs more quickly than a group of Hunter College students. Differences in age, sex, and general intelligence did not affect the rate of conditioning.

A clinical application of the cr method in the treatment of alcoholism has been made by Voegtlin (67), Kindwall & Ziegler (68), and Thimann (69). Aversion was established after five to eight seances in which the beverage was accompanied by a hypodermic injection of emetine. All kinds of spirits must be used, as the patient will acquire an aversion only to the ones which are accompanied by the emetine. Most patients have to return periodically for reconditioning.

Psychosomatic Relationships

The interaction of what has been variously termed physical and mental, body and mind, and more recently, under the sponsorship of Flanders Dunbar, psychosomatic has been studied especially in the past few years in medical laboratories (Cobb, Wolff, Lyman, Binger, Whitehorn and others). Among those who have been making the greatest contribution toward a real objective basis for psychopathology and indirectly toward abnormal psychology is Harold Wolff. From such researches as his, conducted on the basis of a scientific methodology, we may begin to see not

only a simplification but a solution of some of these most intricate of nature's secrets. Dr. Wolff has kindly supplied me with the following summary of his recent contributions here.

The concept of disease as a defense reaction of the organism against hostile elements in the environment has been applied by Harold G. Wolff and his co-workers to their physiologic investigations of psychosomatic disturbances. Concerning nasal symptomatology and disease, observations on the noses of human subjects have shown that hyperemia and swelling of the turbinates, increased secretion and obstruction occur in response to a variety of noxious environmental stimuli including not only those directed at the respiratory passages such as dust and pollens but also to more general threats such as painful constriction of the head by a steel band and even symbolic threats such as discussions in which subjects were made aware of their situational conflicts and frustrations [Holmes, Goodell, Wolff & Wolf (70)]. The nasal response was often linked to weeping with blepharospasm and lachrymation. Taken together these changes appeared to constitute a defense reaction in which an attempt was made by the organism to shut out and wash away the offending substance or situation.

Such a reaction of defense was useful when the threat was from noxious fumes or dust particles but seemed less appropriate against an irresponsible husband or hostile mother-in-law.

Wolff and his co-workers found serious consequences when such an "emergency pattern" as nasal occlusion was unduly sustained. Infection in the nasal and paranasal air spaces often followed. The inflammatory reaction accentuated the already existing swelling and obstruction and thus provided a "vicious cycle" for the self-perpetuation of the disturbance.

Other patterns for dealing with environmental threats involved the stomach. In peptic ulcer, for example, gastric hyperfunction with hyperemia, hypermotility and hyperacidity was found and was interpreted as indicating an aggressive desire to devour or a need for sustenance for the fight. Transitory alterations of such character were noted in numerous nonulcerous subjects during periods of intense resentment. In their well-known fistulous subject (Tom) Wolf & Wolff (71) showed that the hyperemic gastric mucosa was especially fragile and susceptible to erosion during prolonged exposure to gastric juice of unduly high acid content. Here, too, was demonstrated a mechanism for self-perpetuation of the "emergency pattern" of gastric hyperfunction. Contact of acid gastric juice with a mucosal erosion enhanced already existing gastric hyperemia and hypersecretion.

Evidence that the impulses responsible for gastric hyperfunction in response to situational threats reach the stomach via its vagus innervation was adduced by Wolf & Andrus (72). They found, in a fistulous subject, gastric hyperfunction with hyperemia and hypersecretion of acid during anger prior to vagotomy. Following section of both vagi and under identical circumstances this gastric reaction failed to occur.

A contrasting biologic adaptive pattern was found in subjects who were chronically nauseated and frequently vomited. They were found to have hypoactive atonic stomachs. Their pattern seemed to imply a desire to reject and a disinclination to deal with the situation (71).

Not only in the activities of the organs were these various and often contrasting

patterns recognized but also in the attitudes and general behavior of the affected subjects. Thus the sufferer from vasomotor rhinitis, in dealing with his life situation, was a defensive nonparticipator who shut himself off from his problems as he did from the air he breathed. The peptic ulcer patient, on the other hand, was found to be a resentful, aggressive animal and the vomiter a more passive, indecisive individual who rejected challenges as he did his food.

Among soldiers in the combat zone, Wolf (73) found persistent nausea and vomiting associated with hypoactive stomach during fearsome experiences in which the subjects felt overwhelmed.

Hypertension was considered to be another "emergency pattern" in which biologic mobilization for action occurred. A study of hypertensive subjects indicated an offensive drive held in check by a deep seated need to placate and avoid committing hostile acts. These subjects were virtually "sitting on the lid." Sharp decreases in renal blood flow associated with elevation of systolic and diastolic pressures were found in hypertensive subjects during discussion of relevant conflicts (74).

Individuals as a whole were found by Wolff to display conflicting objectives, values and attitudes. In many such subjects were identified conflicting adaptive patterns among their bodily functions. These troubled individuals were truly going in two directions at once. In general, these various patterns of defense, appropriate in certain emergency situations, were found to be costly and often destructive when sustained.

In studying the psychosomatic aspects of peptic ulcer, Finesinger & Weisman (75) found that

Occupational stress, particularly where the individual felt required to work under frustrating, unrewarding conditions or under the direction of a punitive, critical superior, was the most common prevalent situation. Preceding many exacerbations was the feeling that these difficult situations would inevitably lead to failure, with resultant personal humiliation and devaluation. Anxiety and hostility were the most common feelings present in these situations. Anxiety appeared chiefly as worry and feelings of concern centered about the patients themselves or those for whom they felt responsible. Hostility was manifested by suppressed anger, impotent rage, or chronic resentment.

Penfield & Rasmussen (76) have studied the speech centers by stimulation of the cortex in human patients. They conclude that

Vocalization without words has a definite localization in the sensorimotor area of the human cerebral cortex on both sides. . . . Arrest of speech, or the spontaneous statement on the part of the subject that he wanted to talk but could not, was produced by stimulation in much the same sensorimotor areas. This arrest is instantaneous, as though some portion of the motor mechanism needed in speaking were inhibited or were preempted for some other movement.

Stimulation of Broca's convolution of the dominant hemisphere also sometimes produced arrest of speech, but it came without associated movement or sensation, and the patient was apt to explain afterwards, for example, that—"I didn't know what I was counting" or "I could not think."

On the other hand, when a patient was asked for an explanation following

stimulation in the sensorimotor zone, he might say, "I couldn't get my words out," "I felt like stuttering," "could not open mouth," "could not get breath." Production of vocalization by stimulation always interrupted speaking.

Motor elements required in speaking, such as vocalization and movements of lips, tongue, diaphragm, etc., have representation in the sensorimotor cortex of the two hemispheres. Speech may be interrupted by stimulation in either motor "face area," but speech is not abolished by removal of those areas. Stimulation of Broca's convolution does not produce either speech or vocalization, but it may interrupt speech because of interference with what the patient calls thinking.

Organic brain disorder was shown by Wortis & Bender (77) to be characterized by definite patterns of perceptual motor and intellectual functions even though neurological examination failed to disclose signs of a focal lesion.

Bilateral simultaneous sensory stimulation, however, disclosed that the patient perceived only on the left side (phenomenon of extinction). Occasionally, when a stimulus was applied to her right side, she localized the percept to her left side (phenomenon of allesthesia). These phenomena occurred when either her cutaneous, visual, or auditory functions were thus tested. The sensations on the left side were consistently dominant over those on the right side. She also showed marked disorientation in cutaneous, auditory and visual space perception to the right. In conjunction with these sensory changes, her motor functions were also dominant on the left side in that she usually turned to the left side and preferred to use her left extremities. Most sensory and motor performances were ordered to the left. In the sphere of intellectual function her inability to perform a task in which more than one aspect of a situation presented, was dramatic. The perceptual, motor, and intellectual dysfunctions appeared to be related and systematically altered in a definite pattern.

Obesity has been studied from two different points of view by Brooks (78) and Bruch (79). The former showed that in rats with hypothalamic lesions, underactivity had little to do with obesity, while Bruch found that obesity in children not due to endocrine disturbances was practically always a symptom of neurosis or maladjustment, and that such children overate, in contrast to those with organic obesity.

In psychopathic subjects Crandall & Hill (80) found both normal and abnormal subjects respond to some of the test questions by increases in blood pressure occurring within one or two seconds, probably due to vasoconstriction as they occurred too quickly for epinephrine release. The psychopathic patients showed greater irregularity of heart rate and of amplitude than did the normals, with a more prolonged elevation of blood pressure.

Comparing the ability of the normal person and of the anxious patient to hold the breath, Mirsky, Lipman & Grinker (81) found

the average breath holding time in twenty-two normal men was 45 seconds, increased to 86 seconds after one extra ventilation, and to 114 seconds after six ventilations compared to 28 seconds, 55 seconds and 67 seconds respectively in patients with anxiety.

Glutamic acid was found by Zimmerman, Burgemeister & Putnam (82) to accelerate mental functioning, indicated by verbal, motor and Rorshach Tests. The most striking changes occurred in the seriously retarded groups. The greatest improvement was found in abstract thinking rather than in motor skill. Emotional stability was also increased. The children had been followed only six months. Glutamic acid was previously shown by Putnam and others to be valuable in the treatment of petit mal.

Lactic acid was found by Löwenbach & Greenhill (83) to improve depressed patients as measured by sleep, mood and content of thought, suggesting an investigation of carbohydrate metabolism in depression, because work and convulsive therapy which also are remedial agents involve the increase of lactic acid.

Epinephrine has been administered in persistent anxiety states by Cameron (84), based on the premise that the organism is more reactive and that therefore administration of epinephrine for a long period would reduce this reactivity through immunization and consequently the anxiety. Following repeated intravenous doses of 0.001 mg. every ten minutes for a four-hour period there was improvement when reduction in cardiovascular reactivity occurred. Treatment was continued from three months to two years.

The effect of acetylcholine on the central nervous system was studied by Case & Funderburk (85), using physostigmine, prostigmine, atropine, magnesium sulphate, and pilocarpine; only physostigmine and prostigmine affected the conditional reflex, the former abolishing conditional reflex activity for as much as two hours and pilocarpine causing transitory depression and later facilitation of conditional reflexes. The latter result had been found in certain dogs by Freile & Gantt (51).

Adrenal cortical steroid hormones were reported by Riess (86) to improve maze running in the rat.

Teleological Mechanisms

At a conference held at the New York Academy of Sciences October 21st and 22nd 1946, teleological mechanisms were dis-

cussed by L. K. Frank, N. Wiener, G. E. Hutchinson, G. Bateson, W. K. Livingston, P. Lazarsfeld, J. v. Neumann, W. S. McCulloch and A. Rosenblueth. Clonus in the quadriceps extensor femoris is treated as a two neuron reflex by Rosenblueth and collaborators. They found that the oscillation which takes place at six to twenty-five per second may be regarded as a linear oscillation in the logarithm of the number of impulses per second coming through the nerve as well as in the logarithm of the length of the muscle. The synapse is the coincidence-recorder and consequently multiplies rather than adds probabilities. The behavior of the nervous system in general and in clonus especially is largely of an inhibitory-facilitory nature. Clonus was studied as the breakdown of feed-back in a feed-back system analogous to those in nerve mechanism design. Such feed-back systems more complicated than a single degree of freedom often need multiple feed-backs for stabilization; these feed-backs are actually found in the nervous system and they explain the relation between voluntary actions and postural reflexes.

According to Rosenblueth any theory formulated should consider postural adjustments as well as kinetic movements, and the purpose of the movement, since the goal is often a factor. Except for experimental or artificial conditions, the control of movement involves feed-back mechanisms—proprioceptors and exteroceptors—with closed circuits. Myotatic reflexes are the elementary functional units in postural adjustments. Clonus is the breakdown of the tonic reflex. The sequence of physiological events during clonus is as follows:

> Each burst of impulses in the motor nerve elicits a mechanical cycle in the muscle. The phase of contraction stimulates receptors attached to afferent nerve fibers that exert central inhibitory effects; it also depresses the activity of receptors connected with excitatory afferents. During the stage of relaxation the excitatory afferent input grows until the next cycle. The efferent output corresponds to the resultant of the previous central excitatory and inhibitory influences and renews them for the next cycle.

"The results at any moment would depend on what has gone on before," says Rosenblueth. That is, the system is constantly changed by what it is doing. The organism is more like a stream than a lake.

In spite of such amassing evidence for the interrelationships between the autonomic and the somatic nervous systems and the

current concepts of organismal integration in psychiatry represented by the terms "holistic," "dynamic," one should not forget the differences. The reaction of the modern psychobiologist to the absolute entities of the nineteenth century scientist has often erred in the opposite direction, resulting in a confused statement of oneness and unity without due regard to the specific laws of the individual systems. Differences are as important as similarities and interrelationships. The individual members of a unit are in reciprocal relationship at one time or another with most of the other systems of the unit, generally working as a harmonious whole, but as Gantt has shown the conditional reflex and the unconditional reflex, the salivary and the cardiac reactions are not governed by the same laws, and disease and death is the expression of the maladjustments and the failure of perfect adaptations. And our knowledge of psychobiology is still so fragmentary that the following statement of Gerard (87) is hardly exaggerated:

> It remains sadly true that most of our present understanding of mind would remain as valid and useful if, for all we knew, the cranium were stuffed with cotton wadding. In time, the detailed correlation of psychic phenomena and neural processes will surely come; but today we are hardly beyond the stage of unequivocal evidence that the correlation does exist.

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PHYSIOLOGICAL EFFECTS OF RADIANT ENERGY*

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Since the appearance of the last review article on the physiological effects of radiant energy (1), five atomic bombs have been exploded, and a great deal of increased interest in the field of radiation and its biological effects has been aroused. With the development of the atomic energy program considerable impetus was given to investigative work on the physiological effects of radiation and methods which might prove effective in preventing and treating pathological changes induced by radiation. The attempt will be made here to bring out the highlights of recent developments in this field and to mention pertinent work which has been brought out in the past year. Emphasis will be placed on short wave length electromagnetic radiations—x-rays and gamma rays, and on particulate radiations—alpha rays, beta rays, neutrons and fission fragments. Since the subject of ultraviolet radiation has been reviewed recently (2, 3), it will be mentioned only in passing. Genetic effects will be omitted in view of the fact that a review of genetics appears in this volume.

Mechanism of action.—It is generally agreed that alpha, beta, gamma and x-radiations and neutrons produce more or less similar physiological effects (4, 5, 6, 7). However, the efficiency of the various types of ionizing radiations in causing certain biological changes varies considerably (8), and the determination of these differences is of importance not only in testing theories of mechanism but in connection with the problem of health protection of radiation workers. A recent review of the comparative effects of x-rays, neutrons and other ionizing radiations has been made by Gray (9), and of the general biological effects by Spear (10). Early work in this field, which seemed to indicate a dependence of the biological effectiveness upon the specific ionization of a radiation, has been summarized by Hevesy (11) and Zirkle (12). Numerous investigations have been carried out in an attempt to throw light on the mechanism of action of these radiations. In a recent book Lea (13) discusses various possibilities pointing out the problem

* This review covers the period from August, 1946 to August, 1947.

of explaining why such marked biological effects result from doses of radiation which produce only a small degree of chemical change, and in compiling recently gathered information on the inactivation of viruses and effects on bacteria, he (14, 15) presents some of the evidence for both a direct and an indirect action of radiation. Hevesy (11) has reviewed the evidence presented by Dale for an indirect action of radiation, viz., a decrease in the dose necessary to inactivate an enzyme with decreasing concentrations of the enzyme in solution, and the "protective" action of another solute necessitating a larger dose for inactivation, and through studies performed with Ahlström and von Euler demonstrated the suppression of nucleic acid formation in unirradiated rat tumors as an effect of irradiation delivered to unshielded tumors in the same rats. He offers this as conclusive proof of some indirect action of Roentgen rays on cellular division. Using the same technique of measuring radioactive phosphorus uptake in desoxyribose nucleic acid Kelly & Jones (16) have demonstrated an indirect suppressing action on mouse mammary carcinoma from beta ray irradiation of the liver and spleen delivered by a colloidal preparation of chromic radiophosphate.

This indirect action occurring at a site anatomically removed from the tissue being irradiated, effected perhaps by some humoral agent, probably is to be distinguished from the indirect action of the decomposition products of water produced by radiation. Barron (17) points out that recently there have been objections raised against the "hit" theory and more of a tendency to explain most of the physiological effects by actions of these water decomposition products. Forssberg (18) has gathered more information on these phenomena in studies of radiation effects on enzymes, and demonstrated that marked inactivation of catalase may be produced by x-ray doses as small as 5 r. Further evidence favoring an indirect action has been gathered by Halberstaedter & Leibowitz (19) from studies of the fixation of red blood corpuscles in suspension, and by Pickels & Anderson (20) in the irradiation of hemocyanin, although the latter workers point out that some degree of direct action may have taken place, and cite the work of Svedberg & Brohult (21) in which definite direct action of alpha rays upon hemocyanin was demonstrated. Efrati, Bock, & Halberstaedter (22) were able to inactivate tetanus toxin with a dose of seven million roentgens and demonstrated the relative

"protective" action of a number of substances. The effects of x-radiation *in vitro* on nucleic acid and some related substances have been investigated by Sparrow & Rosenfeld (23) and Taylor, Greenstein & Hollaender (24). By measurements of viscosity change a presumably indirect, temperature-dependent effect, which does not seem to be due to the action of hydrogen peroxide, was found as well as a primary effect which was not dependent upon temperature. Van der Werff (25) has reported a further development of his theory of biological action, and Opatowski (26) has presented a theoretical treatment of some aspects of radiation effects and variations in sensitivity.

The physiological effects depend in general upon the amount of energy absorbed per unit volume of tissue and also upon the manner in which the energy is distributed along the individual ionization tracks. This dependence upon specific ionization has suggested the possibility of different mechanisms of action for different types of radiation (27). Barron (28) found that inhibition of the enzyme phosphoglyceraldehyde dehydrogenase by alpha rays (which was 73 per cent complete with 360 r) was partially reversible by treatment with glutathione but the inhibition produced by beta rays and gamma rays was not, and suggested that this reflects perhaps a difference in the biological action of these particles. He concludes that the reversible inactivation by alpha rays involved oxidation of the sulfhydryl groups to disulfide presumably through the action of hydroxyl radicals and hydrogen peroxide produced by the irradiation of water. Beta and gamma rays effected some irreversible change.

Specific Radiations

Neutrons.—Although neutrons and x-rays produce similar effects on tissue, their relative efficiency is different (29, 30). Some investigations along these lines are summarized in a report by Henshaw, Riley & Stapleton (31). These workers in comparing the effects of fast neutrons from the chain reacting pile (1.76 MEV mean energy) to those of gamma rays from Ta^{182} (1.2 MEV mean energy) using the mean lethal dose for mice after a single exposure as a basis for comparison, found one n[1] to be as effective as about 9 r.

[1] The unit of fast neutron dose. One n is the neutron flux that gives the same ionization as one roentgen of x-radiation in a standard Bakelite-wall thimble

Since the energy absorption from one n corresponds to 2.5 rep[2] (27, 33) the lethal effect of a single dose of fission neutrons is 3.6 times that of gamma rays from Te^{182}. When repeated doses were given the neutrons appeared to be much more effective in shortening the life span of mice. 0.25 n was as effective as 8.6 r giving a ratio of 14.

Stapleton & Zirkle (27) made an excellent study of the comparative lethal effects of beta rays from P^{32} (0. 7 MEV mean energy), gamma rays from Te^{182} and fission neutrons on the eggs of *Drosophila*, choosing these test objects because their dimensions are such that they tend to absorb the three radiations uniformly throughout their volume. When their data are combined with that previously obtained by Zirkle on 200 Kv x-rays, one finds, upon arbitrarily taking the biological effectiveness of the beta rays as unity, the effectiveness of the gamma rays to be 1.1, that of the x-rays 1.5, and that of the neutrons 3.1. In comparing the specific ionization of these same radiations in the tissue one finds again arbitrarily taking unity as the value for the beta rays, one for the gamma rays, ten for the x-rays, and two hundred for the neutrons. This work reemphasizes the direct relationship which exists between the specific ionization of a radiation and its biological effectiveness.

This same study also revealed that although the three radiations varied in their biological effectiveness, they were all completely additive so far as the lethal effects on *Drosophila* eggs were concerned, suggesting that the irradiation changes in each case contribute in the same way to the lethal process.

Stapleton & Curtis (34) found a progressive loss of vitality and premature aging in mice exposed to 90 n of fast neutrons (the mean lethal dose for these animals).

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chamber. In England Gray (32) has proposed the unit designated by 1ᵾ and defined as the dose at a point when the associated corpuscular radiations produced in water liberate in air 1 e.s.u. of charge of either sign per 0.001293 g. of air.

[2] The roentgen equivalent physical (rep) is that quantity of ionizing radiation which is capable of producing 1.615×10^{12} ion pairs per gram of tissue or that will suffer an absorption in tissue of 83 ergs per gram. The roentgen equivalent man (rem) is that quantity of radiation which when absorbed by man produces an effect equivalent to the absorption by man of one roentgen of x- or gamma radiation.

Slow neutrons and fission fragments.—Results of studies made of the effects of slow neutrons on mice (31, 35, 36) indicate actions very similar to those obtained with fast neutrons and the conclusion may be drawn that slow neutron irradiation does not have a unique biological action. There are interesting theoretical differences, however, inasmuch as the tissue ionization from a fast neutron beam is produced chiefly by recoil nuclei, mainly protons, resulting from elastic collisions, while the ionization from slow neutrons is produced by transmutation products resulting from nuclei which have captured and reacted with the neutrons.

Early work by Kruger (37) and Zahl (38) using induced transmutations of lithium and boron has been reviewed (29). More recently Tobias, Weymouth & Wasserman (39) have studied the effects of uranium fission *in vivo*. By injecting mice with colloidal preparations containing enriched uranium and subjecting the animals to slow neutron irradiation they demonstrated marked biological effects of the fission. All of the injected mice died after a dose of neutrons which killed none of the control animals. When one considers that the fission fragments have very large energies (about 159 MEV per fission) and a mean specific ionization about thirty times that of polonium alpha particles it is not surprising that large local effects were produced with a few micrograms of U^{235} per gram of tissue. When the calculated fission dose is compared to the beta ray dose from P^{32} in colloidal chromic phosphate used by Jones & Dougherty (40) to produce lethal effects in mice, it appears that the energy from fission recoils delivered to a unit mass of tissue was about twenty-seven times less than that delivered by the beta rays to produce the same effect. Mitchell (41) discusses the tolerance flux of thermal neutrons.

Protons.—An interesting suggestion regarding the use of fast protons in therapy was forwarded by Wilson (42). He proposes the use of a high energy proton beam (150 MEV or more) from a frequency modulated cyclotron. Such a beam could be fanned out or collimated into a very thin pencil, would not scatter appreciably, and could deliver even to a volume as small as one cubic centimeter anywhere in the body a dose of ionization several times that given to any of the neighboring tissues. The radiation effect on the skin would be very much smaller than that in the deeper tissues chosen for irradiation. It may be noted here that recently a deuteron

beam of 200 MEV has been produced in the 184-inch cyclotron in Berkeley by Lawrence and his associates.

Similar and even more startling possibilities are offered by alpha rays and perhaps nuclei of heavier atoms such as carbon should it become practical to accelerate them to high energies. Tobias & Segrè (43) successfully produced a beam of 96 MEV carbon nuclei in a sixty inch cyclotron in 1942.

Beta rays.—In producing physiological effects, x-rays and gamma rays expend their energy in tissue by the ejection of high speed electrons. Hence it has been assumed that the effects of beta rays would not differ essentially. The validity of this assumption was demonstrated by Raper (44) and others with experiments on *Drosophila* eggs and fern spores.

Tissue penetration, however, by beta rays is very limited; when larger animals are subjected to surface irradiation almost all of the energy is absorbed in the skin. Total surface irradiation of laboratory animals with beta rays from P^{32} results in erythema, epilation, desquamation, and ulceration (45) much as found with x-rays.[3] The severity and time of appearance of the effects vary with the dose but are not strictly proportional (47). Damage produced by massive doses (20,000 to 30,000 rep) bears some resemblance to thermal burns except that the various stages require four to seven times as long to develop and the primary action is confined to the epidermis and upper portions of the dermis. There are also differences in the effects on hematocrit and plasma proteins as shown by Anderson (48).

In describing the histopathological changes in irradiated mouse skin, Snider (49) noted swelling of connective tissue cells and breakdown of mast cells as early as three hours after treatment with 5,000 r. This was followed by edema formation and invasion of the dermis with leukocytes. After eight hours there was swelling of the collagenous fibers and while some of the small vessels were occluded, nearby lymphatics and capillaries became dilated. He feels that the persistence of this abnormal condition of the connective tissue may be a factor embarrassing epithelial repair. It might be mentioned here that the relationship of radiation effects

[3] Because of their limited penetrating power beta rays from P^{32} offer a convenient way of giving localized therapeutic radiation to skin lesions. Low-Beer (46) has described a method for their use and gives dosages data.

on connective tissue to overlying epithelium and related malignant growth is discussed by Windholz in an interesting series of four articles in which he also presents some ideas regarding acquired radio-resistance (50 to 53). Microscopic study of autopsy material revealed profound effects on the connective tissue of human larynges which had been given protracted fractionated irradiation for carcinoma. In two cases where the subepithelial connective tissue had been transformed into hyaline sclerotic tissue with obliteration of blood vessels the tumor of the larynx had disappeared. Further emphasis is placed upon the relationship between connective tissue effects and the adjacent tissue by Lasnitzki (54) who subjected mouse adenocarcinoma 63 to two thousand roentgens of x-radiation *in vivo* and *in vitro*. Histological study and mitosis counts showed that the effect manifest during the first day after irradiation was a direct one on the tumor cells but from the second day on an additional effect came into play through damage to the supporting tissue and circulation producing more degeneration *in vivo* than *in vitro*. He estimated one-third of the radiation effect to be direct and two-thirds indirect.

In determining recovery rates after exposure of the skin of mice to beta rays, Raper & Barnes (55) found patterns which were similar to those previously described for human skin erythema produced by x-rays and gamma rays (56, 57, 58). After an initial total body dose of 3,000 rep the half lethal dose of a second irradiation was determined at various intervals. They found half recovery in one and a half to two days and complete recovery in eight days. An interesting and unexplained phenomenon was noted in the period between eight days and sixteen weeks when a recovery exceeding 100 per cent occurred seeming to indicate that a slight degree of immunity against additional exposure had been imparted.

When animals varying considerably in size are given total body surface irradiation with P^{32} beta rays it is found that the mean lethal dose of absorbed energy is directly proportional to the weight of the animal (59). The relationship does not hold nearly so exactly for gamma rays. This result is interpreted by the investigators to mean that beta rays, although they can affect directly only the skin and superficial structures, bring about a lethal result by a total mass or volume effect, while the more penetrating radiations

which in general reach all the tissues do not. It should be further pointed out that in these studies on mice, rats, guinea pigs, and rabbits there was a negligible species sensitivity difference for the beta rays; and it is well known that these same animals differ in their sensitivities to x-rays and gamma rays.

Blood studies on rabbits (60) showed no evidence of either direct or indirect effect and failed to substantiate the claim of lymphocyte stimulation by superficial irradiation. Irradiation of the eyes of rabbits with beta rays from radon resulted in damage to the superficial tissues and secondary iritis (61).

Graff, Scott & Lawrence (100) administered P^{32} parenterally to mice and studied the radiation effects on normal and leukemic tissues. The metabolism and radiotoxicity of P^{32} in mice has been investigated also by Anthony & Snyder (109). Platt (62) found the microscopic tissue changes in patients who had received P^{32} therapeutically to be similar to those produced by x-rays.

It is now possible with the betatron (63, 64) to produce beta rays of very high energy which may prove to be of some value in therapy. However, no biological investigations with these more penetrating radiations have been reported.

Gamma rays and x-rays.—It is well known that a smaller dose of low energy x-rays is necessary to produce skin erythema than of high energy radiation. The physiological effectiveness of twenty million volt and two hundred thousand volt x-rays have been compared (65, 66) indicating that the higher energy radiation is only about 70 per cent as effective as the lower one in producing decoloration of hair in mice, when the physical effectiveness as measured by a Victoreen r-meter is considered to be identical. The question of the density of ionization is possibly involved.

The effects of chronic low intensity irradiation are particularly interesting in view of the increasing use of atomic energy, radioactive materials, and radiating machines of various kinds. Mice, guinea pigs, and rabbits have been given daily low level total body irradiation with gamma rays over long periods of time (67, 68). No significant damage to the hematopoietic system of mice was noted with daily doses of 1.1 r given for a period of over three years. Radiation damage was discovered histologically in the gonads of animals exposed to 4.4 r per day, and the females of one strain were permanently sterilized at this dose rate after receiving

about 465 r. Animals reared and maintained while getting daily doses of 1.1 r and 0.11 r gave no evidence of damage to chromosomes. Five or six subsequent generations bred and reared in the exposure fields were normal with regard to litter size and life span.

The extremely interesting finding was made that at all dose levels (8.8 r, 4.4 r, 2.2 r. 1.1 r, and 0.11 r per day) including the lowest there was a decrease in the life span of irradiated mice. This was accounted for in the higher dose groups chiefly by early appearance of malignancies and damage to the hematopoietic system. However the mechanism whereby life was shortened by the low dose remains obscure. In mice at least there seems to be no age variation in radio sensitivity (72).

Boche (73) in studying the effects of chronic x-radiation on animals finds that with long lived species no effects on survival can be shown with doses below 1 r per day when the radiation is given for only a fraction of the animal's normal life. However, with large enough doses (about 10 r per day for dogs) he finds that the increase in mortality is proportional to the dose, the same interesting relation which obtains for smaller animals.

No damage to the testes of animals exposed to continuous low level radiation was noted with a daily dose of only 0.11 r (67), but with the larger doses effects on the spermatogenic elements was seen. The interstitial tissue was not visibly affected histologically by accumulated doses as high as 5,000 r. While testicular effects were dependent on the dose rate rather than the total dose, damage to the ovaries depended on the total dose and was irreversible. The follicles decreased in number and finally disappeared. Ovaries proved more sensitive than testes showing definite effects at levels of 1.1 r per day; however considerable species variation was noted. A comparison of radiation effects on the ovary with naturally occurring changes associated with the natural history of follicles has been made by Halberstaedter & Ickowicz (74).

The hematopoietic system of the guinea pig is very sensitive. All animals receiving 8.8 r per day, and many of those getting 2.2 r per day died of anemia with thrombocytopenia. The bone marrow demonstrated varying degrees of hypolasia. Again species variation was marked. Alterations in the blood picture of rabbits was found only in the group receiving 8.8 r per day. No damage was visible in the bone marrow of mice subjected to this type of irradiation

even after the maximum accumulated dose of 5,800 r. Craver (75) was unable to find ill effects on the blood counts or clinical states of eight patients with advanced cancer who received ten to fifteen roentgens of total body radiation per day amounting to 150 r and 300 r, which could not be ascribed to the disease. Five cases were followed from four to nineteen months after irradiation. He concludes that healthy persons could well tolerate such doses. This is not to be confused with the so called "tolerance dose" of x- and gamma radiation (76) which is agreed upon as 0.1 r per day.

Simon-Reuss & Spear (77) have found that many cells which show recognizable histological abnormalities after gamma irradiation in tissue culture are capable of completing mitotic division within the normal time limits. The effects of *in vitro* irradiation of rabbit spermatozoa on embryonic development are discussed by Amoroso & Parks (78). Further observations on the effects of x-ray on cells *in vitro* have been made by Schreck (79).

On the basis of favorable clinical results obtained with ascorbic acid in the treatment of radiation sickness Kretzschman & Ellis (80) determined blood levels on patients and on rabbits. Patients undergoing x-ray therapy and the experimentally irradiated animals both showed decreased levels of ascorbic acid. Ellinger (81) obtained a protective action against radiation effects on the liver with desoxycorticosterone and offers this as evidence in support of the histamine hypothesis of radiation action.

The question of protection against radiation is reviewed by Parker (82) and in a report by the Standardization Committees of the American Roentgen Ray Society and the Radiological Society of North America (83).

Special Biological Effects

Effects on blood and hematopoietic tissue.—Extremely interesting results have come from the investigations by Allen and coworkers (84, 85, 86) of the hemorrhagic phenomena caused by radiation in dogs. Animals receiving 450 r total body x-radiation, although they seemed in good health for the first ten days, developed marked prolongation of the clotting time by the sixth day and spontaneous hemmorhages in the mouth and rectum by the ninth. Points of needle puncture bled freely, even those made several days previously; and blood failed to clot in the test tube.

At this stage of the reaction platelet counts were in the neighborhood of 260,000. Prothrombin deficiency and fibrinogen deficiency were likewise ruled out as causes of the hemorrhagic disease. Replacement therapy with vitamin K, calcium salts, and transfusions were ineffectual. Furthermore, the clotting time of normal dog blood was prolonged when amounts of the abnormal blood were added. However, upon the addition of known antiheparin substances such as toluidin blue or protamine the normal clotting time was restored. The investigators were able to isolate from the blood a substance with the properties of heparin.

It is important to note here that in the presence of hyperheparinemia the prothrombin time is invalid. Although in this study prothrombin times were occasionally found to be prolonged, all the animals showed normal prothrombin times when plasma was first treated with toluidin blue.

Considered in the light of Allen's investigations a report such as that made by Kaufmann (87) on the blood changes associated with low level chronic exposure to x-rays, although perhaps subject to somewhat different interpretations, takes on added meaning. He summarizes a seven-year survey of the personnel of a hospital radiology department pointing out that blood cytology is not a sufficiently sensitive indicator of the effects produced by repeated minimal doses of radiation, and concludes from his studies of various hematological tests performed on these people that prolongation of the prothrombin time is perhaps the most critical indicator of minimal damage.

There has been a certain amount of difference in opinion regarding the changes manifest by the blood after irradiation. Ostro & Macht (88) found normal platelet counts and prothrombin times, but reported a reduction of the coagulation time of the blood as a general effect of x-rays whether the irradiation is carried out *in vitro* or *in vivo*. On the basis of these findings two patients with hemophilia were given splenic irradiation, and reduction of the clotting times reported. This interesting result is difficult to evaluate since marked response was obtained in only one patient and there is a characteristic variation in the clotting times in this disease. Dunlap (89) states that there is evidence to indicate that moderate doses of radiation cause an increase in the number of circulating platelets and that by this and other changes the clotting

power of the blood is increased for a short time. Heavy irradiation on the other hand reduces the platelet count and results in the tendency to bleed.

In a summary of radiation effects on hemopoiesis, J. S. Lawrence, Dowdy & Valentine (90) bring out clearly the fact that evidence is lacking for a direct action on the formed elements of the peripheral blood except when radiation is given in huge doses and that changes in the peripheral blood are determined in large measure by the length of life of the various morphological components and the radiosensitivity of their parent cells. The circulating corpuscles, cells, and platelets present at a certain time disappear from the circulation according to the so-called rate of utilization which can be determined experimentally. Since the turnover time for white blood cells in the cat is about twelve hours, for platelets about five days, and for red corpuscles probably about one hundred and twenty days, the radiation effects noted by changes in blood counts are readily explainable. These various points are also well reviewed by Cantril, Jacobson & Nickson (91) who state that the beginning of a marked drop in circulating lymphocytes has been seen within one hour after a total body dose of about 50 r. The rates of depression of the formed elements show a tendency to approach their respective rates of utilization. After a single dose of radiation which destroys a fraction of the marrow erythroblasts one may be unable to detect changes in the red count since the long life of the circulating corpuscles tends to obscure a small damage while at the same time the marrow is rapidly recovering. That erythroblasts are very radiosensitive has been shown by Bloom & Bloom (92) who found them to diasppear from the marrow earlier than myelocytes after a half lethal dose of x-radiation. This was true for rabbits, mice, rats, and chickens. Similar results were obtained with irradiation by fast and slow neutrons and a variety of radioactive isotopes. Jacobson and coworkers (93) being interested in radiation effects on pre-existing anemia, produced regenerative anemia in rabbits with repeated bleeding and with phenylhydrazine. Administration of 800 r of total body x-radiation failed in each group to produce further anemia or seriously interfere with the recovery of the animals. Bone marrow studies showed a marked stimulation of erythropoiesis in the anemic animals which subsequently tolerated the large doses

of x-ray apparently because a sufficiently large number of erythroblasts survived to maintain adequate blood formation.

In an effort to find distant effects on hematopoietic tissue from local irradiation J. S. Lawrence and his co-workers (90), joined normal cats for long periods of time to irradiated cats by carotid anastomoses at various intervals after the doses were administered. No evidence of such an effect was obtained. They report work by Rekers and his associates in which dogs were given radiation to the whole body with the exception of single shielded extremities. Possibly a slight compensatory hyperplasia of the nonirradiated marrow was obtained. When the lower extremities were given very large doses of radiation and the rest of the body shielded, marked radiation damage was found in the irradiated marrow and other tissues of the hind legs but a negligible change noted in the peripheral blood.

Immunity.—An interesting mechanism for the action of radiation on immunity is supported by Dougherty & White (94), who suggest that through both a direct effect and an indirect hormonal effect x-radiation brings about dissolution of lymphocytes which is accompanied by increases in total serum proteins and gamma globulins. These phenomena are associated with an anamnestic response in previously immunized mice. A 200 r dose of total body x-radiation produced this complex in adrenalectomized animals; a dose of 10 r failed but brought out the effects in normal mice. They propose a pituitary-adrenal cortical control of lymphocyte dissolution (95) and through the endocrine mechanism a certain control on serum levels of gamma globulins and antibodies. The indirect action of x-rays, it is postulated, is effected through the endocrine mechanism and the direct one through direct radiation damage to lymphocytes in lymphoid tissue.

Glenn (96, 97) reports a sevenfold increase within twenty-four hours in the phagocytic indices (*Staphylococcus aureus* as the test organism) of rabbits given 100 r of x-rays. The indices rose from an average of 9.6 to an average of 65.0 in one day, then fell to 40.0 at the end of three days and to 25.0 at the end of four. He observed as well that the effect of the same roentgen dose delivered at fifty to ninety kilovolts was not nearly as effective as when delivered at one hundred and forty. Likewise an increase in the kilovoltage to two hundred and above diminished the effect. It is of

interest here to note that in 1944 Bisgard and co-workers (98) demonstrated the elaboration of a nonspecific antitoxin in rabbits after irradiation. Failure to produce the antitoxin by irradiation of rabbit blood *in vitro* was taken as evidence that the material was produced in the tissues.

Allen (84) has noted that after large doses of x-ray to dogs a marked susceptibility to infection develops with the prolongation of clotting time and appearance of hemorrhage. Although the data are too scant to allow definite conclusions, the attractive suggestion was made that the anticoagulant is present normally in the blood in combination with immune proteins, and as a result of the heavy irradiation the biological integrity of the latter is destroyed and the heparin-like substance freed. This supposition was strengthened by the protection against bleeding given to irradiated dogs by injections of hyperimmune serum.

On the basis of the hypothesis that an hemolytic antibody might be the important factor in chronic acquired hemolytic anemia Evans & Duane (99) irradiated the mediastinal and periaortic nodes of two patients suffering with this disease. In one case remissions were noted when transfusions were combined with the radiation. Although no conclusions can be drawn from this preliminary work, it represents an interesting approach to the problem.

Carcinogenic effects.—It has long been known since the experience of early workers with x-rays that radiation can be carcinogenic. Henshaw & Hawkins (101) found leukemia to be 1.7 times as common among physicians as in the general male white population and March (102) found the incidence in radiologists to be ten times that among physicians not practicing radiology. The high incidence of osteogenic sarcoma among the radium dial painters has been linked to radioactive deposit in the bones. Recently Brues, Lisco & Finkel (103) in investigating the carcinogenic action of various radioactive substances produced a high incidence of bone tumors in mice after single and repeated injections of radiostrontium (Sr^{89}). An incidence of 80 per cent was found with monthly doses of one microcurie per gram of body weight. In addition to the bone tumors various lymphomas appeared.

Copp, Axelrod & Hamilton (104) have shown that most of the radioactive fission products and the heavy long-lived alpha ray

emitters are deposited and remain in the skeleton for long periods of time. A 25 per cent incidence of bone tumors was found in mice with chronic doses of plutonium amounting to one tenth of a microcurie per gram of body weight (103). Bloom *et al.* (105) have suggested the possibility that radioactive carbon (C^{14}) may remain in the skeleton for long periods of time. If this is true carcinogenic effects would not be surprising in view of the long half-life of this isotope; no published work has reported such tumors as yet.

Lawrence (106, 107) and others who have used radioactive isotopes in therapy for many years have reported no cases of cancer induction in treated patients even though many have received repeated doses, especially of P^{32}, over a number of years. In general the doses used have been much lower than those used in tumor induction in animals. The therapeutic use of radioactive isotopes has recently been reviewed (108).

In their studies of the effects of long continued gamma irradiation of laboratory animals, Lorenz *et al.* (67) found carcinogenic action mainly in mice, although rabbits and guinea pigs developed some tumors after about three years of irradiation. The induction of malignant lymphoma in mice seemed to be dependent on the total dose and dose rate. Larger doses produced earlier appearance of tumors. Other tumors frequently seen were carcinomas of the lung, ovary, and mammary gland. The ovarian tumors are of special interest since their incidence was considerably increased with as low a daily dose as 0.11 r, and they seemed to be the result of an irreversible degenerative process which started with the depletion of follicles.

Kaplan (110), from some preliminary studies of radiation-induced lymphoid tumors in mice, has suggested the possibility of an interesting hormone relationship.

Raper, Henshaw & Snider (111) produced epithelial tumors of the skin, fibrosarcomas, and mammary carcinoma in mice and rats after single exposures to beta rays, the optimum dose lying between 4,000 and 5,000 rep. Prolonged daily irradiation with beta rays (112) at a level of 50 rep per day produced an increased incidence of subcutaneous tumors in rats, and after nine months of such treatment mice showed some ulceration of the skin and precancerous activity No effects on these animals were found with rates of 5.0 rep per day.

A rest period of a month or more between two subcarcinogenic doses of ultraviolet radiation was found by Rusch & Kline (113) to decrease the incidence of induced ear tumors in mice whereas a rest period up to one month had no appreciable effect in differentiating the results from those of continuous irradiation provided the total dose was the same.

The possible role of somatic mutation and plasmagenes in the etiology of cancer has been reviewed by Kamen (114) in a report on the use of radioactive isotopes as tracers in the study of radiation effects. He also reviews briefly work indicating the similarity of x-ray induced mutations and those produced by mustard gas and the nitrogen mustards (115, 116). On the basis of these studies and those of Latarjet (117) who showed the same chemical changes in the cell to be produced in some instances by x-ray ionization and by molecular activation with ultraviolet, he points out the plausibility of assuming common metabolic changes in the production of malignancy whether radiation or chemical causes are involved. Of interest in this connection is the work of Strong (69, 70, 71) who produced changes in coat color and tumor incidence with methylcholanthrene.

The fact that an increased incidence of chromosome breaks is found in *Tradescantia* when x-ray is preceded by infrared irradiation has suggested to Swanson & Hollaender (118) that possibly some structural change or "sensitization" may occur with the infrared so that effects of subsequent x-irradiation are increased.

Figge (119) has formally brought up the question of cosmic ray effects in carcinogenesis, presenting the results of a study made on mice which he interprets as evidence that cosmic ray showers produced in lead plates over the cages cause an earlier appearance of tumors in methylcholanthrene treated animals.

Effects of the atomic bomb.—It is estimated that some eighty thousand people died in Hiroshima and forty-five thousand in Nagasaki as a result of the two atomic bombs used in combat, and it has been further estimated that 20 per cent of them died of irradiation. A number of papers have appeared describing the effects on people (120 to 124). In general it may be said that the effects of the ionizing radiations which were liberated in incredible amounts were essentially similar to those known to follow exposure of experimental animals to large doses of x-rays, gamma rays or

neutron rays, or a combination of these. From results of investigations in 1935 and 1936 with neutrons and gamma rays of approximately the same energy from a cyclotron one could pretty well have predicted the radiation effects of the atomic bomb (6). Henshaw (125) for example, has described death within a few hours of single total body exposures to 50,000 r of x-radiation. There seemed to be generalized toxemia, shock, and hyperthermia. Histological study showed that widespread tissue destruction had occurred in the short intervals with extensive cytoplasmic and nuclear degeneration.

In addition to the gamma rays and neutrons given off at the time of the explosion there were large amounts of infrared, visible light, and ultraviolet. Larkin (126) in a study made in Nagasaki reports that superficial effects from such radiations were by far the most widespread in that city being found one and a half miles from the center. Flash burns affected only exposed surfaces, shadows being sufficient to protect the skin except in zones close to the explosion where burns occurred beneath clothing. Those at great distances from the center felt no heat but noted burns several seconds after the explosion.

The type of radiation effects varied with distance from the explosion. There were few survivors at Nagasaki within six tenths of a mile; the survivors between this distance and eight tenths of a mile showed the maximum effects of ionizing radiation; beyond this there were severe superficial burns but penetrating radiation effects were less prominent.

Since exposed persons received total body radiation survivors were those who received less than 500 r as pointed out by Warren (121), and the effects noted were on the more radiosensitive organs. The two major causes of death (124) in those who survived the explosion were damage to the hematopoietic tissue and severe diarrhea and vomiting which accompanied damage to the gastrointestinal tract epithelium. Severe leukopenia was seen in the first few days as reported by Japanese workers. Most of the leukopenic deaths occurred in the first three weeks after the bombing (121). Hemorrhagic phenomena were widespread and were a major cause of death between the third and fifth weeks. It is interesting in the light of Allen's work (84) to note that Keller (127) reports finding increased bleeding times but normal clotting times. The possibility

must be borne in mind, however, that an hyperheparinemic condition may have gone unnoticed in those dying of hemorrhages earlier and that patients showing normal clotting times and increased bleeding times were manifesting the effect of thrombocytopenia due to marrow depression. Hypoplastic and aplastic anemias were very common. Keller also reported the occurrence of disturbed liver function, albuminuria, tyrosinuria, hypoproteinemia, jaundice, and fever. Retinal hemorrhages were characteristic (128, 129, 130).

In reporting the effects on animals at the Bikini tests, Draeger & Warren (131) point out the expected similarities to those observed in Japan and to the serious radioactive contamination problem created by the underwater detonation.

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